THE BRITISH VETERINARY JOURNAL

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Vol. 113 **March, 1957** **No. 3**

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EDITORIAL

PLAN FOR THE FUTURE

In the last issue of this journal we were able to comment upon the splendid progress that had been made towards the eradication of tuberculosis from amongst the cattle of this country. The campaign now coming to a successful conclusion illustrates the benefits which follow an organised attack upon a disease when its etiology and pathogenesis has been elucidated. Tuberculosis is not the first disease to succumb under such circumstances. Cholera, bubonic plague, typhoid, glanders and rabies are serious and lethal diseases which have been brought under control and in some cases eliminated in those countries where adequate measures have been taken. The control and ultimate eradication of a lethal or crippling disease is a matter of the utmost importance in the realms of public health for a disease may incite repercussion far beyond its own immediate effects. The ill that is done is not always immediate and manifest. Sometimes the effects can be likened to a continuous attrition which in time leads to a state of chronic sub health. Tuberculosis may take a virulent and fulminating form or it may follow a silent but insidious course. In most instances it is not a "killer disease" and some degree of tolerance can be established between the victim and the disease. It is as if the patient and the disease were being weighed and neither could tilt the balance and win. The afflicted one is not manifestly ill but neither is he completely well for his metabolism and resistance are taxed to the utmost to preserve a *status quo.*

When the body's defences are strained to withstand one enemy and resistance and resilience are low other enemies can attack with little let or hindrance. Much ill health and loss of efficiency is occasioned in this manner in men and animals who are the victims of some other primary disease. It

(The February issue of The British Veterinary Journal was published on February 12)

is obvious that when tuberculosis is eliminated from our herds many of the minor ills of cattle will tend to fade away and the services of veterinary surgeons will not be in such constant demand either for the direct attack upon tuberculosis or for the treatment of the lesser troubles which flourish under its shade.

This may give rise to serious economic effects upon veterinary practice and especially upon those veterinary surgeons who devote most of their attention to the treatment of illness in cattle. For the last 15 years the profession has experienced an era of prosperity greater than has been known before. There is no doubt that this salubrious state of affairs has stemmed primarily from the work which has been allotted by the government to veterinary surgeons employed in the scheme for the eradication of tuberculosis. In most practices a strange anomaly can be observed. There are no more clients than there were in 1938, but much more work. Most of that work has been in connection with the tuberculosis eradication scheme. The amount of work has been so great in many areas that practices which provided only a modest living for one man have developed so that several people have been able to enjoy lucrative employment.

As the eradication scheme has approached to full fruition and areas have been cleared there have been signs already of a diminution in the demands for veterinary services and in some cases it has been necessary to dispense with the services of assistants.

Whilst any sensible man will welcome the abolition of tuberculosis one cannot ignore the fact that if there is no disease it will not be necessary to employ people to eradicate it. This may have serious repercussions on the veterinary profession. The period of prosperity has attracted great numbers of young people to a career in Veterinary Science. The number of graduates has almost doubled in the last 10-15 years. They have been able to find employment with ease because of the tuberculosis eradication scheme. If work in this sphere should come to an end or even if it were diminished appreciably many veterinary surgeons will be "out of work." If the services of only one assistant in each practice were dispensed with, between 500 to 600 veterinary surgeons would be in search of employment and the number would be constantly increased as the schools disgorged new graduates.

The very success of the tuberculosis eradication scheme presages a grave situation which will confront the profession unless other means of employment can be found. This can be done quite easily and with inestimable benefit to the community. Tuberculosis is not the only disease which should be eradicated from our flocks and herds. Johne's disease for example is probably the cause of greater economic loss than tuberculosis. Abortion, infertility and parasitic infestation are other problems which call urgently for investigation control and final eradication.

The conquest of tuberculosis is an example of a job done well and a testimonial to the work and value of an efficient veterinary service. There are plenty of other fields to conquer and as tuberculosis fades from the picture, plans should be laid for the conquest of another enemy and incidently to ensure that there will be plenty of work for the profession for many years to come.

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GENERAL ARTICLES

THE TREATMENT OF CHRONIC CARRIERS OF *SALMONELLA PULLORUM* WITH FURAZOLIDONE

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CONSIDERABLE attention has been given to the evaluation of furazolidone in the control of *S. gallinarum* and *S. pullorum* infection in chickens and turkeys (Grumbles, Wills and Boney, 1954; Williams Smith, 1954*a* and 1954*b;* Cosgrove, 1954; Harwood and Stunz, 1954; Harbourne and Sellers, 1955, and Wilson, 1955). All these workers have been concerned with its efficacy in reducing mortality during active, and in most instances experimentally produced, outbreaks of these diseases and they have drawn attention to the fact that the carrier rate among the recovered birds is low.

Williams Smith (1954*b*) reported that foci of *S. pullorum* infection in chicks that were chronic carriers were sterilised by furazolidone therapy, while Harbourne and Sellers (1955) suggested that the drug might be of value in eliminating *S. gallinarum* infection from carrier birds. Gordon and Tucker (1955) have reported that this compound showed considerable promise in eliminating *S. pullorum* infection from naturally infected adult carriers. When furazolidone at both 0.02 per cent and 0.04 per cent was fed continuously for 10 days in the rations of 13 birds positive to the rapid whole blood test in the field, 11 were subsequently found to be free from *S. pullorum* infection. All of the untreated controls showed generalised *S. pullorum* infection. The majority of treated birds showed a decrease in agglutinins after the cessation of treatment but in most instances the birds did not give a negative response to the blood test until between 60 and 84 days after treatment. The value of the drug as a supplement to the blood test in eliminating carriers, in reducing the number of retests in heavily-infected flocks and as an added ensurance of freedom from infection in hatchery supply flocks was discussed.

Harwood (1954) states that "treatment with furazolidone reduces the reactors to the usual pullorum-type blood test by 75 to 90 per cent but seldom eliminates them. Flocks of chickens and turkeys to be retained for breeding purposes should be blood tested, the reactors removed and the remainder treated with furazolidone. This combination of blood test and drug is reported to have performed satisfactorily for the elimination of reactors in several field trials." Gordeuk (1956), in a review of the National Symposium on the Value of Nitrofurans in Agriculture, states that a report from Massachusetts predicts that pullorum disease may be completely eradicated from the U.S. by a programme involving the present blood-testing system plus furazolidone.

Wilson (1956), however, found that the feeding of furazolidone at 0.04 per cent in the mash continuously for 12 days to birds with agglutinins against *S. pullorum* failed to induce a significant or permanent lowering of the agglu-

tination titre, while in 20 out of 26 treated carriers, *Salmonella* persisted after treatment, the commonest site of infection being distorted ovules. On the other hand the treatment had a marked preventive effect on the laying of infected eggs, only two of 466 eggs laid after treatment (0.4 per cent) contained *Salmonella* compared with an infection rate of 30.9 per cent (69 of 223 eggs) laid before treatment.

Present Investigation

This investigation is an extension of our preliminary report (Gordon and Tucker [loc. cit.]) and includes:

(1) An evaluation of the efficiency of furazolidone in the treatment of naturally or artificially affected carriers of *S. pullorum;* this is based on the examination of treated birds at intervals after treatment and comparisons made with untreated controls.

(2) An examination of the serum agglutinin titres of treated and untreated naturally and artificially infected carriers of *S. pullorum.*

(3) The effect of treatment on the bacterial content of eggs laid by natural and artificially-induced carriers, compared with that of eggs laid by untreated carriers and on the transmission of *S. pullorum* in fertile eggs, in dead-in-shell chicks and in chicks hatched from the treated and untreated groups.

(4) The results of a field trial made in collaboration with a commercial hatchery, on the elimination of carriers from *pullorum* infected supply flocks by flock treatment with furazolidone after the removal of carriers at an initial routine blood test.

Materials and Methods

Carrier Fowls: (*a*) One hundred naturally-affected carriers of *S. pullorum* detected at routine blood testing were obtained from 10 different hatchery supply flocks. In order to establish the presence of *S. pullorum* infection in the flocks concerned, 20 fowls, representative of the various groups, were sacrificed on their arrival at the laboratory and immediately after their serum agglutinin titres had been ascertained. The remaining 80 carriers were divided in two groups and housed in fold units with slatted-floor runs and raised off the ground on concrete piers. The birds in Group A, consisting of 28 fowls, were maintained throughout the experiment as untreated controls and slaughtered at intervals varying from 40 to 140 days after their arrival at the laboratory. Group B, consisting of 52 fowls, was treated for 10 days with furazolidone at a concentration of 0.04 per cent in the mash. These fowls were examined at intervals of five to 120 days after the beginning of treatment. The results from these groups are shown in Table I.

All eggs laid before and during treatment by both groups were examined bacteriologically. Prior to treatment a Brown Leghorn stock cockerel was introduced to each fold unit and from the end of the treatment period all eggs were retained for incubation. These stock cockerels originated from the Station's control flock and had all given negative reactions to the agglutination test. The results are shown in Tables V and VI and summarised in Table VII.

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(*b*) *Artificially-infected carriers.* A total of 268 R.I.R. x W.L. chicks were inoculated *per os* at day old, three weeks old and four weeks old with *S. pullorum* broth culture plus alkali powder by the method described by Williams Smith (1954*b*).

Fifty-two chicks died within the following four weeks and *S. pullorum* was recovered from all. At 16 weeks of age 60 survivors (28 pullets and 32 males) showed agglutinins in their serum; the non-reactors were discarded. These 60 carriers were divided into two groups and housed in slatted-floor fold units. Thirty-four birds constituting Group A were maintained throughout as untreated controls and sacrificed at intervals of 0 to 44 days after the start of the treatment of Group B. The 26 fowls in Group B were treated for 10 days with 0.04 per cent furazolidone and examined post-mortem at intervals varying from 14 to 44 days after the start of treatment. The results are shown in Table II, while the combined results of the treatment of natural and artificially-infected carriers are shown in Table III.

All eggs laid by both groups were examined bacteriologically, but no eggs were retained for incubation from the artificially-infected carriers. The results are shown, together with those from the naturally-infected carriers, in Tables V and VI and summarised in Table VII.

Medication. In all cases treatment was carried out by the addition of furazolidone at a concentration of 0.04 per cent to the standard layers' rations used at the Houghton Poultry Research Station (Williams Smith, 1956). The drug as a proprietary pre-mix* was mixed in the ration for 30 minutes by means of an electric Hobart mixer at the rate of one lb. per one cwt. This medicated mash was fed for 10 days, all other food being withheld. The mixer was "earthed" in accordance with the mixing instructions of A. J. White, Ltd. (1956), which states that "it is important that the mixer should be electrically grounded to prevent the attraction of particles of nitrofuran compounds to the wall of the mixer by static electricity which would hinder proper mixing and that mixing operations should continue for not less than half an hour." Harwood (1954) states that "since furazolidone crystals are sensitive to electrostatic forces, caution should be observed in mixing the drug and that in one instance a feed mixture labelled to contain 0.04 per cent furazolidone failed to control experimental 'blackhead' in turkeys. Analysis showed that the portion of the feed used contained no detectable furazolidone; grounding the mixing equipment gave better results."

Examination of organs for the presence of S. pullorum. Portions of liver, heart, spleen, gall-bladder and intestines were ground in a mortar containing sterile sand and incubated in 250 ml. Selenite F medium (Hobbs and Allison, 1945) at 37° C. for 24 hours. Subcultures were made on to plates of desoxycholate-citrate agar, containing 1 per cent each of sucrose and salicin (Williams Smith and Buxton, 1951), which were incubated at 37° C. for 24 hours and examined for *S. pullorum.*

* Neftin.

Examination of eggs and dead-in-shell chicks. In the case of fresh eggs the shell and contents were separated and each placed into screw-capped jars containing Selenite F medium and incubated for 18 hours at 37° C. The shell was removed from dead-in-shell chicks and placed into jars of Selenite F medium. The contents of the shell were macerated by cutting with sterile scissors and placed in approximately 250 ml. of Selenite F medium and the whole suspension incubated for 18 hours at 37° C.

Examination of hatched chicks. During incubation the eggs were placed in individual muslin bags. When hatched the chicks were wing-banded and

TABLE I

Isolation of S. pullorum from Naturally infected Carriers of S. pullorum disease. Treated with 0.04 per cent. Furazolidone and from Untreated.

	Time of autopsy in days after start of treatment of Group B	No. of fowls	State of ovary at autopsy		S. pullorum isolated	Sites from which S. pullorum isolated						
			D	N		O.	Ovi.	L.	S.	H.	S.B.	Int.
Group A. UNTREATED	0 days	20	9	11	17	15	9	10	6	6	6	3
	40-140 days	28	13	15	24	13	7	15	8	6	10	7
	Total 0-140 days	48	22	26	41	28	16	25	14	12	16	10
Group B. TREATED	5 days	5	3	2	1	-	-	-	-	-	-	1
	11 - 40 days	21	8	13	NIL							
	50 - 120 "	26	9	17	1	-	-	-	-	1	-	-
	Total 5 - 120 days	52	20	32	2	-	-	-	-	1	-	1

placed in wire-floor electrically-heated brooders. The shell residue was cultured as described in Selenite F medium. The chicks were reared for three weeks when all survivors were sacrificed for examination. All chicks, including those which died during the three-week period were examined as follows : the yolk sacs, hearts, portions of the liver and intestines were transferred to test tubes containing 30 ml. Selenite F medium and incubated for 18 hours at 37° C. Sub-cultures from eggs, dead-in-shell chicks and from organs of hatched chicks were then made on to desoxycholate-citrate agar plates as previously described.

Agglutination tests. Agglutination tests were made at weekly intervals by the serum-tube method at dilutions of 1 in 25, 1 in 50, 1 in 125 and 1 in 250. The results are summarised in Table IV.

Results

(1) *The efficiency of furazolidone based on the bacteriological examination of treated and untreated, naturally and artificially infected-carriers of S. pullorum.*

Table I shows that *S. pullorum* was isolated on autopsy from 41 out of 48 (85.4 per cent) untreated fowls of Group A; these had reacted to the routine

whole-blood test. There was no evidence of spontaneous recovery of the untreated fowls while at the laboratory since the percentage recovery rate of *S. pullorum* of 85 per cent (24 out of 28 fowls) retained throughout the experiment and slaughtered at intervals of 40-140 days after the start of treatment of Group B, was the same as that of the birds sacrificed on arrival at the laboratory (17 out of 20 birds examined). Furthermore, the untreated fowls showed generalised infections and the organisms were isolated from the ovary, liver, oviduct, gall-

TABLE II

Isolation of S. pullorum from Artificially Infected Male and Female Carriers of S. pullorum Disease, treated with 0.04 per cent. Furazolidone and from untreated Controls.

	Time of autopsy in days after start of treatment of Group B	No. of fowls	State of ovary at autopsy		S. pullorum isolated	Sites from which S. pullorum isolated.							
			D	N		O.	Ovi.	L.	S.	H.	G.B.	Int.	Testis
Group A UNTREATED	0 days	12	NIL	12	8	3	0	6	3	4	5	2	-
	14 - 44 days	22	3	13	19	10	6	9	8	5	6	9	-
	0 - 44 days	34	3	25	27	13	6	15	11	9	11	11	-
Group B TREATED	14 - 44 days	26	3	9	3	0	0	2	2	2	1	2	1

bladder, spleen, heart and intestines. Nearly 50 per cent of the untreated birds showed degeneration of the ovary and in all such cases *S. pullorum* was isolated from that organ.

Of the 52 naturally-infected carriers treated with furazolidone, *S. pullorum* was isolated from two only (approximately 4 per cent). In one bird the organism was recovered from the heart wall and in the other from the intestines. Despite the fact that 20 of the 52 treated carriers showed macroscopically degenerated ovaries the organism was not recovered from that site. *S. pullorum* was isolated from one only of five birds slaughtered five days after the commencement of treatment. Since in this case the organism was present only in the intestines it is reasonable to assume that a complete recovery might have ensued. All of the 21 fowls slaughtered within one month of the cessation of treatment were free from infection.

The autopsy findings of the 60 artificially-infected carriers are shown in Table II. *S. pullorum* infection was established in 27 of the 34 untreated fowls of Group A (79 per cent) compared with 3 of the 26 treated fowls of Group B 11.5 per cent). Again, there was no evidence of spontaneous recovery in the untreated group over the experimental period, and infection was of a generalised nature. Two of the three infected birds in the treated group showed generalised infection. The organism was not recovered from the gonads of Group B (treated) but although only three of the fowls in the untreated group A showed macroscopic ovarian degeneration, *S. pullorum* was isolated on 13 occasions (50 per cent of infected birds) from that organ.

A summary of these findings are shown in Table III from which it will be seen that of 78 chronic carriers of *S. pullorum* treated with 0.04 per cent furazolidone for 10 days 73 or 93.6 per cent were free from infection on autopsy, compared with 14 of 82 non-treated carriers (17.1 per cent), maintained over

TABLE III

Summary of Tables I and II Showing Isolation of S. pullorum from Treated and Untreated, Naturally and Artificially Infected Carriers of S. pullorum.

Treated or untreated	No. of fowls	State of ovary at autopsy		S. pullorum isolated	Sites from which S. pullorum isolated.							
		D	N		O.	Ovi.	L.	S.	H.	G.B.	Int.	Testis
UNTREATED	82	25	51	68 (83%)	41 (50%)	22 (26%)	40 (50%)	25 (30%)	21 (25%)	27 (33%)	21 (25%)	-
TREATED	78	23	41	5 (6%)	- -	- -	2 (2.5%)	2 (2.5%)	3 (3.8%)	1 (1.2%)	3 (3.8%)	1 (1.2%)

Figures in brackets shown approximate percentage isolations.

the same period. Conversely, the infectivity rate of un-treated carriers was 82.7 per cent compared with 6.4 per cent in a similar number of treated birds.

(2) *Effect of furazolidone therapy on the agglutinin titres of chronic carriers of S. pullorum.*

Agglutination tests were made at regular intervals and autopsies were made at varying intervals and the results cannot be given in simplified tabular form. The attempt made to summarise the findings in Table IV shows that contrary to the findings of Wilson (1956), furazolidone treatment had a marked influence on the reduction of agglutinin titres of carriers of *S. pullorum.* The titres of the 82 untreated fowls in Group A at the beginning of the experiment were 1 in 250 (19), 1 in 125 (21), 1 in 50 (30), 1 in 25 (12), none was negative. There was a marked upward trend in the titres in eleven birds when autopsied up to 140 days later, while none showed a decrease. The converse occurred in the treated birds of Group B. Before treatment 30 had titres of 1 in 250; 28, 1 in 125; 13, 1 in 50; and 7, 1 in 25; while none was negative. Even after five days treatment two birds showed a reduction, one from 1 in 250 to 1 in 125, and one from 1 in 125 to 1 in 50. During the month after treatment 10 fowls only maintained titres of 1 in 125 or over, as against 58 originally at this level, while 15 fowls had become negative. Of the 26 fowls kept for periods of two to four months after treatment, 18 gave negative reactions to the blood test and none had titres of over 1 in 50. In other words, 33 of the 78 fowls (approximately 42 per cent) retained for up to 120 days after treatment failed to show the presence of agglutinins to *S. pullorum,* while in 44 (56 per cent) there was a marked decrease in titre at the higher levels.

(3) *Effect of furazolidone therapy on the bacterial content of eggs laid by carriers of S. pullorum and on the transmission of infection in incubated eggs.*

All eggs laid by the 80 naturally-infected birds and by the 28 artificially-infected pullets before therapy was started were either cultured or retained for incubation and the results are shown in Table V. *S. pullorum* was isolated from 14, or approximately 1.2 per cent, of 1,192 eggs laid by the 108 pullets. A

TABLE IV

Serum Titres of Treated and Untreated Naturally and Artificially Infected Carriers of S. pullorum disease.

	Time in days in relation to treatment of Group B.	No. of fowls with serum titre shown					Total
		1:250	1:125	1:50	1:25	NEG.	
Group A UNTREATED	At autopsy 0-140 days after treatment of Group B.	27(19)	24(21)	19(30)	12(12)	0(0)	82
Group B TREATED	5 days after treatment.	2(3)	1(1)	2(1)	0(0)	0(0)	5
	11-40 days after treatment	4(21)	6(14)	73(7)	9(5)	15(0)	47 / 78
	50-120 days after treatment	0(6)	0(13)	3(5)	5(2)	18(0)	26
TOTAL		6(30)	7(28)	18(13)	14(7)	33(0)	-

further 289 eggs laid by the naturally-infected carriers were incubated. Unfortunately, one of the stock cockerels proved relatively infertile and 192 eggs were infertile or contained dead embryos. *S. pullorum* was isolated from five

TABLE V

Isolation of S. pullorum from Fresh and Infertile Eggs, Dead-in-Shell Chicks and Chicks hatched from Naturally and Artificially Infected Carriers of S. pullorum Prior to Treatment.

How infected	No. of fowls	No. fresh eggs cultured	S. pullorum isolated	No. eggs incubated	No. infertile & D.I.S.	S. pullorum isolated	No. chicks hatched	S. pullorum isolated	Total S. pullorum isolated
NATURALLY	80	830	10	289	192	7	97	6	23
ARTIFICIALLY	28	362	4	-	-	-	-	-	4
TOTAL	108	1192	14	289	192	7	97	6	27

of the 122 infertile eggs (4.2 per cent) and from two of the 70 dead-in-shell chicks (approximately 3 per cent). Seventeen of the 97 chicks hatched died and *S. pullorum* was isolated from the visceral organs of one chick. Five other chicks yielded *S. pullorum* from their intestines (6 per cent). The remaining chicks were sacrificed 21 days after hatching but no evidence of *S. pullorum* infection

was found. A similar procedure was carried out on the eggs laid by the birds in the furazolidone treated and in the untreated groups and the results are shown in Table VI.

It will be seen that *S. pullorum* was isolated from three of the 391 eggs laid by the 44 untreated fowls (0.76 per cent), but was not recovered from the 620 eggs laid by the 64 treated pullets. *S. pullorum* was isolated from seven of the 221 infertile eggs or dead-in-shell chicks from the 307 eggs incubated from the

TABLE VI

Cultural Examination of Fresh and Infertile Eggs, Dead-in-shell Chicks and Chicks Hatched from Naturally and Artificially Infected Carriers of S. pullorum after Treatment with 0.04 per cent. Furazolidone and from Untreated Controls.

	How Infected	No. fowls.	No. fresh eggs cultured	S. pullorum isolated	No. eggs incubated	Infertile & D.I.S.	S. pullorum isolated	Chicks hatched	S. pullorum isolated	Total S. pullorum isolated
UNTREATED	Naturally	28	337	3	307	221	7	86	16	26
	Artificially.	16	54	NIL	-	-	-	-	-	-
	Total	44	391	3	307	221	7	86	16	26
TREATED	Naturally	52	555	NIL	178	100	NIL	78	NIL	NIL
	Artificially	12	65	NIL	-	-	-	-	-	-
	Total	64	620	NIL	178	100	NIL	78	NIL	NIL

untreated group (3 per cent), while 16 of the 86 chicks hatched from the untreated group yielded the organism from their intestines or tissues (18 per cent). No evidence of *pullorum* infection was established in the infertile eggs, dead-in-shell chicks or chicks hatched from the 178 eggs incubated from the treated group.

In Table VII the results of the examinations of the eggs laid before treatment (Table V) have been added to those from the untreated Group A of Table VI and compared with the data shown for the eggs laid by the pullets treated with furazolidone (Group B, Table VI). It will be seen that *S. pullorum* was isolated from 17 of 1,583 eggs laid by untreated carriers of *pullorum* disease (approximately 1 per cent); from 14 of the 413 infertile or dead-in-shell chicks (3.3 per cent); from 22 of the 183 chicks hatched (12 per cent). A total of 53 isolations from 2,179 examinations (2.4 per cent). *S. pullorum* was not isolated in the course of the 798 examinations made of eggs, dead-in-shell embryos or hatched chicks from the treated pullets.

(4) An extensive field trial was carried out by one hatchery during 1954-55 with the following results. In a total of 78,779 birds tested in 96 flocks, 200 reactors were disclosed in 31 flocks in numbers varying from single reactors in a few flocks to 37 reactors in the most heavily-infected flock. Approximately

2 per cent of the birds were examined and *S. pullorum* isolated from all. These reactors were removed from the flocks concerned and the remaining non-reactors fed for ten days on a mash supplemented with furazolidone at 0.04 per cent. The first retest of the 31 reactor flocks was made from two to three weeks after treatment and four reactors only were disclosed. These birds were examined post-mortem and *S. pullorum* recovered from the tissues of two. At a subsequent

TABLE VII

Summary of Tables V and VI Showing Incidence of S. pullorum in Eggs, dead-in-shell and Chicks Hatched from Carriers of S. pullorum Prior to and After Treatment with 0.04 per cent. Furazolidone and from Untreated Controls.

	No. eggs cultured	S. pullorum isolated	No. eggs incubated	No. infertile & D.I.S.	S. pullorum isolated	No. chicks hatched	S. pullorum isolated	Total S. pullorum isolations
TREATED	620	NIL	178	100	NIL	78	NIL	NIL
UNTREATED	1583	17 (1%)	596	413	14 (3.3%)	183	22 (12%)	53 (2.4%)

Figures in brackets show approximate percentage isolations.

re-test of all of these reactor flocks none gave positive reaction. The histories of five of the flocks are summarised :—

Flock C. At an initial test in October, 1954, nine reactors were disclosed in 502 birds tested. Furazolidone was fed and at a re-test three weeks later one only reactor was disclosed. This bird was submitted for examination which failed to reveal the presence of *S. pullorum*.

Flock H. This flock had been responsible for a number of outbreaks of pullorum disease in 1952-53 and despite repeated testing during that season a clean flock was not obtained. At an initial test in October, 1954, 30 reactors were disclosed in 1,565 birds tested. Furazolidone was fed, after removal of the reactors, and at re-test three weeks later no further reactors were disclosed. The flock was again treated in February, 1955, as a further safeguard and when tested as a yearling flock in August, 1955, one single reactor was disclosed in 1,169 birds tested. On submission for examination this bird showed no evidence of *S. pullorum* infection. Chicks were hatched from this flock continuously from November, 1954, until autumn, 1955, with no evidence of pullorum disease.

Flock D. Initial test showed 18 reactors in 1,427 birds tested. Re-test four weeks after feeding furazolidone showed no reactors present.

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Flock E. Initial test disclosed 22 reactors in 717 birds tested. Re-test four weeks after feeding furazolidone showed no reactors.

Flock F. On an initial test on 650 birds two reactors were disclosed, no drug treatment was used and on re-test a further 10 reactors were found. Then furazolidine was fed and on re-test, one day after the cessations of treatment a single reactor was disclosed. When this bird was examined bacteriologically, *S. pullorum* was isolated from the liver, heart, ovary, oviduct, spleen, intestines and from an egg in the oviduct.

Discussion

When 78 naturally and artificially infected carriers of pullorum disease were treated with 0.04 per cent of furazolidone in the mash for ten days *S. pullorum* was isolated from the tissues of five (6 per cent); it was isolated from 68 (83 per cent) of the 82 untreated carriers. The infection was of a generalised nature in the untreated carriers and the organism was recovered from a number of sites and this varied from 50 per cent recoveries in the ovary and liver to 30 to 25 per cent from the spleen, oviduct, heart, gall-bladder and intestines. Although macroscopic degeneration of the ovary was present in about a third of the treated birds, the organism was not recovered from that site whereas it was recovered from half of the ovaries in the untreated group.

About 42 per cent of the treated fowls failed to show evidence of agglutinins to *S. pullorum* when tested up to 120 days after treatment; there was a marked decrease in the titres in 56 per cent of those examined at autopsy compared with the titres before treatment. The untreated birds showed no decrease in titres and none became negative to the agglutination test.

Eggs laid by treated and untreated birds were examined and 17 of the 1,583 eggs laid by the untreated group (1 per cent) yielded *S. pullorum* whilst the organism was not recovered from 620 eggs laid by the treated group. Five hundred and ninety-six eggs were incubated from the untreated carriers and *S. pullorum* isolated on 36 occasions (6.0 per cent) from infertile eggs, dead-in-shell chicks or from the chicks hatched. None was isolated from the incubated eggs or chicks hatched from the 178 eggs incubated from the treated group.

These findings conflict to some extent with those reported by Wilson (1956) who showed that although furazolidone exerted a considerable bactericidal effect on *S. pullorum* and *S. gallinarum* in carriers, in that in only two treated birds could the persisting infection be termed widespread, nevertheless in 20 out of 26 treated carriers, *Salmonellæ* persisted in distorted ovules after treatment. Further, Wilson found that although the treated carriers showed a distinct drop in titre, in most cases it was of a temporary nature and after a few weeks the titre resumed its normal level. This latter discrepancy is possibly of little importance since the continued persistence of agglutinins was probably associated with the fact that infection persisted in the distorted ovules.

It is difficult to suggest a reason for the conflicting results in the two experiments concerning the persistence of infection in degenerate ovules, since there

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is more or less complete agreement between the two experiments with regard to the effect of furazolidone treatment on the laying of infected eggs. No infected eggs were laid by the treated carriers in the present experiment, while in that quoted by Wilson (1956) only two of the 466 eggs laid after treatment (0.4 per cent) contained *Salmonellæ* compared with 69 out of 223 eggs laid before treatment (30.9 per cent). The two positive eggs in Wilson's experiment came from one bird which had laid 13 infected eggs out of 15 during the three weeks before treatment.

This prevention of infection of the egg is emphasised by the lack of transference of infection via the hatching egg. *S. pullorum* was not isolated from dead-in-shells, infertile eggs or chicks hatched from eggs laid by treated fowls compared with the moderately high level of infection in the eggs and chicks from the untreated group. Infection was present in as many as 12 per cent of chicks hatched from the untreated group; had this occurred under field conditions, a widespread outbreak of the disease would be expected.

A possible explanation of the discrepant results might lie in the relative ages of the carriers used; in Wilson's (1956) experiment, infection had been of long standing producing grossly distorted ovules. As Wilson suggests, either the *Salmonellæ* in the distorted ovules are too numerous to be overcome completely by the action of the drug or that, possibly as a result of a diminished blood supply to the diseased ovules, the drug may not be available in sufficient concentration. As he points out, the effects of the drug on the organism elsewhere in the ovary is profound. In this test the naturally-infected carriers were derived from pullet flocks at a primary routine test and in at least one case the history suggests that infection may have been acquired recently.

However, the persistence of infection in distorted ovules would not necessarily be of great importance in field conditions, since as Wilson has shown, such birds continue to react positively to the routine test and would be detected and removed. In any case, since both in this and in Wilson's experiment *S. pullorum* was not isolated from normal ovules or from the eggs laid by treated carriers even when infection persisted in distorted ovules, such fowls would be unlikely to be responsible for egg-borne infection, for grossly degenerated ovules are seldom if ever laid as eggs (Gordon and Garside, 1946).

As Wilson pointed out, the most valuable property of the drug in the treatment of carriers of *S. pullorum* would be in the prevention of the laying of eggs containing this organism and as an added insurance of freedom from infection in flocks supplying hatching eggs. The present experimental and field results quoted would support this contention. We are, nevertheless, strongly of the opinion that the drug should not be considered as an alternative to routine blood testing but rather as an adjunct to it. Furthermore, Cooper and Skulski (1956) have shown that furazolidone will produce testicular changes when fed at 0.04 per cent for 21 days and that feeding the drug above this level results in aggravated changes mainly in the amount of fibrous tissue which causes the disappearance of seminferous tubules. Whether such changes are of a permanent

nature or whether they would result in a marked effect on fertility was not determined. It would seem, therefore, that this drug should be used with caution and that, as already discussed, the greatest care must be taken to ensure that proper mixing is carried out. The drug has no adverse effect on egg production (Cooper, 1956).

The procedure recommended is that subsequent to blood testing and the removal of reactors, the non-reactor flock should be treated with 0.04 per cent furazolidone in the mash for 10 days; all other food should be withheld and that a further blood test should be made three to four weeks later in order to detect any persisting reactors.

The present experiment indicates that such a method should materially decrease if not eliminate the laying of infected hatching eggs from infected flocks and thereby reduce the potential risk of continued infection in the progeny. It would be reasonable to assume that the complementary use of drug therapy and blood testing may well accelerate the reduction of *pullorum* infection on a national basis. Certainly, its intelligent use can be of benefit in speeding up the elimination of infection in hatchery supply flocks in that experience would indicate that fewer re-tests of infected flocks are required and that hatching eggs can be safely used at an earlier date from treated flocks from which reactors have been removed. It also offers advantages in the treatment of infected flocks when husbandry methods are such that movement of the non-reactors to new premises is impossible.

Summary

1. The feeding of 0.04 per cent furazolidone in the mash for 10 days to birds whose sera reacted to the agglutination test for *S. pullorum* resulted in the removal of infection from 73 out of 78 naturally and artificially infected carriers of *S. pullorum* (94 per cent); 83 per cent of untreated carriers remained infected.

2. Forty-two per cent of the treated birds failed to show the presence of agglutinins to *S. pullorum* when retained for 120 days after treatment, while in 56 per cent there was a marked decrease in titre. No reduction in titre occurred in the untreated controls.

3. *S. pullorum* was not recovered from 620 eggs laid by treated carriers nor from the dead-in-shells or chicks hatched from 178 eggs. Conversely *S. pullorum* was recovered from 17 out of 1,583 eggs laid by untreated controls, from 14 out of 413 infertile and dead-in-shell chicks and from 22 out of 183 chicks hatched from a total of 596 eggs incubated from the untreated controls.

4. The result of a field experiment carried out in collaboration with the supply flocks of a hatchery indicated the value of this treatment in the elimination of infection from infected flocks.

5. The application of furazolidone therapy in the eradication of pullorum disease is discussed.

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BOVINE CYSTIC OVARIAN DISEASE—A REVIEW OF RECENT PROGRESS

Article 1

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Basic Features

Adrenal Virilism: Adrenal, Anterior pituitary, Urine excretion, Ovaries, Uterine pathology, Body conformation, Behaviour.

Nymphomania: Adrenal, Anterior pituitary, Ovary (structure of cyst, contents of cyst—direct evidence, indirect evidence, discussion), Urine excretion, Remainder of genital tract (uterine pathology; cervix, vagina and vulva; blood picture; general physical features and behaviour).

Question of Intermediacy.

Incidence of disease by breeds, percentage incidence, economic importance.

Ætiology: Heredity, Effects of environment (nutrition, milk yield, conclusions), Experimental induction of disease.

Therapeutics: Treatment by manual rupture, Hormonal therapy, Combined rupture and hormonal therapy, Control of treatment, and Prognosis.

Summary.

For at least since 1831 (Garm, 1949*b*) a clinical entity has been recognised in the cow. It is characterised by infertility, usually permanent, associated with the production of large ovarian cysts (as distinct from neoplasms), and usually accompanied by impairment of the cyclic activity of these organs and by some alteration from normal sexual behaviour. Lesbouyries (1944) considered he was the first to differentiate within this syndrome between nymphomania, an exacerbation of the feminine character, on the one hand, and on the other a frank virilism; a distinction abundantly confirmed by later workers.

Adrenal Virilism

The study by Garm was the most detailed; he observed fuchsinophilic granules in the *adrenal tissue* (a characteristic of the hyperplastic adrenal which is the commonest cause of human virilism), associated with four times the normal level of *urine androgen excretion*, biologically assayed (1949*c*), and very high 17 Ketosteroids as microchemically estimated. Lesbouyries analysed, for *œstrogens* only, urine from one such case, and found them absent. His view that androgens were secreted *by the ovary* fails to tally with Garm's results, nor did he seem to be aware that ovarian androgen secretion was only a rare cause of the disease in women. The anterior pituitary lobes in Garm's study (1949*d*) were normal.

As regards the *ovaries*, Lesbouyries claimed that characteristically cysts were absent, whereas Garm found they were present, though not invariably; his earliest (1947*a*) paper assumed their presence in all cases. These cysts contained luteal

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tissue in the wall, which, Garm suggested, might be characteristic, in view of the recognised luteinising effect of cortical androgens in the rat. Here one may compare the occurrence of the luteoma, a rare corpus luteum-like ovarian tumour which is one cause of virilism in the human; what hormones are secreted is an interesting question (L. Berger, 1945). The luteal type of cyst, in association with relative anœstrus (absence of feminine behaviour) has been recognised also by Berthelon (1946), Koch and Berger (1954), Ajello (1947), and by Yamauchi and Inui (1954), which is consistent with Garm's finding in his more complete differentiation of the two types. Yamauchi described well the disappearance of the granulosa layer, and progressive luteinisation of the theca interna in such cysts, the contents of which were invariably œstrogen-free.

No associated *uterine pathology,* beyond some degree of retrogression, appears to have been described in established cases of adrenal virilism. *Body conformation* is described by Garm as essentially masculine, and his photographs show beefy thighs and thick neck as might be expected. Curiously they also show, as described, too, by Lesbouyries, a markedly raised tailhead, presumably associated with slackened pelvic ligaments—this is a somewhat puzzling feature.

Both these authors also stress an over-development of the clitoris, a rational result of masculinisation, but whereas Garm does attribute this to androgen production, Lesbouyries, though favourable to such a conception, claims to have cured the whole syndrome in a number of cases by a simple clitoridectomy, and suggests that mechanical irritation by a retained cereal awn might be solely responsible. Koch and Berger describe a very well marked masculinisation of the body shape; in their observations associated with luteal cysts (though also with follicular cysts accompanying nymphomania). They mention a shrunken vulva as part of the masculinisation syndrome, in marked contrast to the swollen one recognised widely in connection with nymphomania cases, including their own.

Sonnenbrodt and Ranninger (1949), describe the appearance of a bull-like neck (accompanied with raised tailhead) in a small proportion of their " cystic " cases, giving no details about the cyst structure : however, these authors noted in these cases, as well apparently as in others, a striking degree of masculine *behaviour,* including deepened voice, digging with their horns, pawing the soil, driving the other cattle and digging up fence stakes. Masculine behaviour is also stressed by Garm, who mentions (1949*b*) laryngeal structural change accompanying the " breaking " of the voice. Lesbouyries noted this also. In contrast, Ajello reports " nymphomania " and glandular cystic hyperplasia in association with a single ovarian cyst of luteal type. As this was a second-hand report, however, *masculine* behaviour may well have been exhibited by this case—the homosexual behavious of the œstrous cow proving a fertile source of confusion. Insufficient pains have been taken by many observers to distinguish between the bellowing of œstrus and the deeper utterance in the bull, and, in the case of virilism, between the cow which will chronically " stand " as well as jump and the virile cow which only " jumps." Vandeplassche (1951) specifically mentions, too, that some cows affected with virilism become dangerous to approach; compare Garm's alleged " alteration in temperament."

Adrenal. As regards the morphology, Hirt and Szeky (1954) describe (in a group of infertile cows which exhibited either cystic follicles or atresia) the common features in this gland, as compared with controls, as being an increase in the proportion of chromaffin cells with strongly vacuolated cytoplasm in the medulla; and in the cortex, besides an increase in cells with hyperchromatic nucleus, containing lipoid, there were also patches of tissue staining more deeply for fat. Garm (1949*b*) mentions that the adrenals were much enlarged in his nymphomania cases, and were free of fuchsinophilic granules, but they contained birefringent crystals similar to those observed in follicles—see below. He considers this to indicate some type of increased activity of the zona glomerulosa. This tissue is known to be to some extent concerned with the regulation of the electrolyte and fluid balance of the animal. In this way he accounts not only for certain changes in the genitalia but also for the salty taste of the milk produced (as recorded in the older literature, and by Vandeplassche). The bitter taste and dark colour of the meat, recorded by Laggi (1955), must be another effect. The neutral steroids of the urine were determined by Garm in 16 cows and gave an average daily excretion level less than half that of 14 controls. The evidence from this author's " virilism " series is strong, that these steroids are secreted by the adrenal, since the typical granules were found there and also some of the cases showed atrophy in the obvious alternative (ovarian) site. Thus in nymphomania, the adrenal hypertrophy is accompanied by *subnormal* function in one respect at least.

Anterior Pituitary. Hypertrophy was asserted to occur independently by Garm (1949) and Paredis (1950); Garm found a mean increase of 40 per cent in weight/volume in 27 nymphomaniac cows while Paredis's figure was from 50 to 100 per cent. Garm noted that the colloid mass in the residual lumen was considerably larger in the affected cows, an observation fully confirmed by Hirt and Szeky in up to 15 animals. Paredis found no change in the cell-type proportions except a decline in the small basophiles. Hirt and Szeky found removal and degranulation of acidophil cells but could detect no characteristic difference in the basophiles. Garm was the first to describe hyaline basophiles and hypertrophic amphophiles in this situation, which he claims are pathological forms of basophile and increase in proportion, along with the large basophiles. These observations appear to be not inconsistent with Paredis's, and perhaps with the drop in acidophils observed by Hirt. Garm remarks that there is evidence that the basophiles secrete FSH, LH, LTH and corticotrophic hormones.

Yamauchi, Ashida and Inui (1954*b*), using a different terminology,, found in 6/6 hypophyses a doubling in the proportion of " β cells "; they quoted their own experimental evidence that the β cells produced FSH, so it seems justifiable to identify them with the large and hyaline basophiles which Garm also found in increased proportion. Possibly the drop in small basophiles observed by Paredis may be due to their conversion by pathological process into the hypertrophic amphophile type observed by Garm.

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Paredis carried out analysis of the anterior pituitary hormone content but could find no departure from normal. Yamauchi, *et al.*, however, dried the glands and claim to have determined the gonadotropic potency, respectively for FSH and LH, by bio-assay; the minimum dose to give a positive reaction for each hormone being termed the Potency Index, and the P.I. for FSH divided by the P.I. for LH being termed the Gonadotropic Quotient for that animal. They claim an average G.Q. of 3.0 for the nymphomaniac (controls unity) and hence deduce that the proportion of FSH to LH was increased threefold. The G.Q. value was observed to coincide with the extent of the rise in β cells, thus tending to confirm Garm's statement that these (large basophiles?) are the source of FSH, LH, etc., and increase in this disease at the expense of other cell types.

Ovary:

	Cases	Percentage Incidence R.	L.	Bilat.
Danelius, 1944	97	46	12	39
Vandeplassche, 1951 ...	100	65	35	—
Garm, 1949*b*	100	31	19	50
Roberts, 1955	100	33	23	44

A number of workers have reported the distribution of the cysts as between the two ovaries; the table provides examples and shows that the superior activity of the right ovary, generally accepted in the normal animal, is maintained in this disease.

The Structure of the Cyst. Much work was done on this aspect by the earlier students, whose results are well summarised by Garm (1949*b*). Romiti expressed the general consensus of opinion in a phrase: "The successive degeneration of ovum, membrana granulosa, and theca interna." In Garm's material the membrana granulosa was in the later stages found to be thinning, and the theca interna degenerating, though the basal portions of the cysts were sometimes lined with a very thin layer of luteal tissue. Hirt and Szeky also mention the epithelium becoming cubical and up to two layers thick, which may imply luteinisation. They describe in detail the progressive thinning and cell-impoverishment of the theca interna. Yamauchi and Inui (1954*a*) saw the same changes in follicular cysts from anœstrous cows, but their findings in nymphomaniac cows were in marked contrast to the foregoing results, namely, an unusually thick granulosa layer and a highly vascular theca interna. It is interesting that Dubreuil (1941) described a similar structure of ovarian cysts in human material, cysts whose origin was attributed to corpus luteum deficiency. These, too, exhibited a membrana granulosa which was thickened (12 to 20 cells deep) and an hypertrophied theca interna. Ajello also described a granulosa several layers thick in follicular cysts.

Besides the thin luteal linings in some nymphomaniacs' cysts, Garm also observed distinct islets of luteal tissue in some cysts and follicles (though Ajello considered such tissue elements were, in fact, old luteal remnants, in apposition to cysts which developed later). Garm considered there was some sort of cyclic

activity in a number of his cases which showed a periodicity of œstrus signs. That such periodicity may have been associated with development and regression of a corpus luteum is suggested by Vandeplassche's dissection of four nymphomaniacs' ovaries, which include besides typical cysts, a seemingly normal corpus luteum; Gruber (1952), also found three such animals though they may not have been nymphomaniac. Two similar cases observed by Yamauchi had large cysts but were anœstrous in life.

Little recent work is apparent on the condition of small multiple cysts of the "grape bunch" type. From the remarks of Berthelon, and the numbers encountered by Gruber, and Hœckner (1952) they are much the less common type.

Contents of the Cyst: Direct Evidence: Lesbouyries was able to demonstrate a "moderate" œstrogen content in three samples of follicular fluid, which must, on his evidence, have been considerably greater than that in the normal œstrous follicle, but Berthelon demonstrated no œstrogen in the fluid when he attempted to repeat this. Garm also failed to demonstrate the presence of œstrogens in any material from his series of nymphomaniacs (1947*a*), though the photometric test used gave satisfactory results with stallion urine. However, Yamauchi claimed to have assayed biologically the œstrogen content of the cysts in 10 nymphomaniac cows, finding in at least one cyst in each animal levels of 833 to 4,000 international mouse units per litre as compared with an average of 432 i.m.u. in the œstrous follicles of 10 normal controls. The divergency of results between Lesbouyries and Berthelon was clarified by Yamauchi's finding that almost half the cysts from the nymphomaniac cases did not yield œstrogen titres, in this way resembling the follicular cysts from two anœstrous cows he tested.

Indirect Evidence: Sonnenbrodt and Ranninger noted in their clinical cases that milk yield fell when œstrous symptoms became prolonged, an effect that can be produced by synthetic œstrogen administration. Koch and Berger noted, in addition, a temporary rise in yield following the rupture of the cysts. This strongly suggests that œstrogen is secreted by the cysts into the system and that rupture in some way arrests this process. Garm observed certain birefringent crystals in normal interœstrous follicles, which disappeared during heat, inducing the supposition that œstrogen was secreted continuously but stored in crystal form, until mobilised for heat production. Such crystals were absent from the cysts of active nymphomaniacs, suggesting that hormone was absorbed into the system as fast as it could be produced. However, in a proportion of cysts in which degeneration of granulosa and theca interna was very evident, the birefringent crystals could be observed, and some correlation was possible with remission of the external physical symptoms of nymphomania. This sequence may be interpreted as a final degeneration of the cells of the cyst wall terminating œstrogen production, with also some storage of the last quota produced, suggesting that the flow to the general body system is maintained by "secretion rate pressure." Yamauchi's (and Dubreuil's) observations that the theca interna and granulosa are hypertrophied in active nymphomania confirm this concept

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with some force, as does also the Japanese finding that nearly half the cysts in active cases have both degenerate walls and œstrogen-free contents. The concept is thus reached that a typical case of the disease goes through a phase of active nymphomania during which cysts succeed one another in attaining an active peak of œstrogen secretion and then degenerate, though they may persist. Later quiescence may supervene, when all the cysts, large and persistent though they may be, are more or less inactive. Alongside such cases there may be others; probably those in which some corpus luteum-forming ability is retained, in which, as Garm believes, œstrogen production is intermittent—"cyclic."

Discussion: It is interesting that Garm also observed similar birefringent crystals in the adrenal glands, especially as their occurrence marched with that of the follicular crystals, so that presumably the peak abnormal activity of the adrenal, disturbing electrolyte balance, coincided with peak œstrogen level in the general body system. In this connection, Garm (1949*a*) draws attention to Selye's success in inducing cortical hypertrophy by experimental administration of œstrogens to laboratory animals. Thus the adrenal changes would be secondary to the ovarian ones, themselves presumably secondary to those in the anterior pituitary. Hancock (1949) also drew attention to this work of Selye's; and he put forward the view that cases of cystic disease failing to show heat signs, lacked the progesterone component, which there is evidence is synergistic with œstrogens in heat production; alleging that œstrogen must be present, nonetheless, in such cysts. Garm's and more especially Yamauchi's work on their content and structure must tend to confute such a view. Hancock's suggestion that, in the normal animal, progesterone protects the adrenal cortex against the effects of continuous follicular œstrogens may well be correct, and it would be interesting to know the state of the adrenals in the cases of cystic disease which retain the ability to form corpora lutea.

Urine Excretion: Various workers having confirmed that only towards the end of pregnancy does the normal cow show any detectable urine œstrogen excretion, Lesbouyries was able to demonstrate positive urine reactions of a similar strength in the same nymphomaniac subjects from which he obtained follicle œstrogen; though Garm failed here he succeeded in demonstrating in 14 nymphomaniacs a urine *androgen* excretion only about half the normal. Yamauchi and Asida claimed to have estimated quantitatively œstrogens occurring in the urine of normal œstrous controls, and to have found similar levels in urine of two "anœstrous cystic cases," and levels four to five times as high in the urine of three active nymphomaniacs, thus confirming the earlier French work, but as Yamauchi also claims, to be able quantitatively to follow fluctuations in bovine urine *pregnandiol,* these results, representing so great a technical advance on all others' work in this field, may have to be regarded with caution until more details are available.

Remainder of Genital Tract

Uterine Pathology. Garm (1949*b*) studied the uteri from 62 cases, finding 49 per cent over-all, and 57 per cent from continuous strong heat animals, to

show enlargement. This he attributes to œdema resulting from the adrenal cortical pathology. Histologically, there was usually some degree of cystic dilatation, giving the extreme "Swiss cheese" effect only in the odd case, and infiltration of the wall with lymphocytes and plasma cells. He observed only two cases of "inflammation," with a muco-purulent exudate, and recovered organisms, of the normal uterine type, and in small numbers, only six times in 52. Garm remarked on the relatively slight abnormality of this series of organs, as contrasted with that reported in the earlier literature, mentioning that more invasion and proliferation by components of the normal bacterial flora, might have been expected in a body thus flooded with œstrogen. Appropriately in the same year the present writer (Dawson, 1949) described a high incidence of cystic ovarian disease in a series of cows affected with purulent catarrhal endometritis and pyometra, of which the histopathology was described, associated with *Corynebacterium pyogenes,* a normal flora constituent having pathogenic properties when combined with a precipitant factor.

The success of Weinstein, Gardner and Allen (1937) in producing experimental pyometra in mice, with invasion of normal vaginal flora, by flooding the system with extraneous œstrogens, was recalled in this connection. Further recent contributions on the incidence of relatively gross uterine pathology were provided by Hoeckner (1952) who recorded 20 cases of cysts of which 10 exhibited uterine disease; Gruber (1952), "most" of whose 21 cystic cows, and a similar proportion in a larger number of heifers, were so associated; and Grandchamp (1953), who treated 11 cases for cysts, all of which were actively discharging pus. Neither Hoeckner nor Gruber cut any sections, so the signs of disease they record must have been of a gross nature. Gruber independently suggests an ætiology along the lines of Weinstein's experiment, and Romiti (1955) actually discusses this mouse work in connection with his own research on cystic ovaries. Ajello found glandular cystic hyperplasia and dilatation in his uterine sections, equally associated solely with luteal, as with follicular ovarian cysts. Cultures were made by Gruber and Hoeckner, but not by Grandchamp. These are not correlated with the type of disease which they accompanied.

Cervix, Vagina and Vulva: Garm describes the discharge of œstral mucus as a common but not constant feature, the cervical canal as usually open, and, in the chronically œstrous cases, the cervix itself was much enlarged. Only two other recent writers describe the appearance of the cervix, which on general grounds one would expect to simulate those of œstrus. Rather earlier, Day (1943) also described cervical enlargement as characteristic. But Hancock (1949) suggests that œstral mucus production and cervical opening are typically poor in the absence of a *normal genital phase succession,* which seems somewhat at variance with Garm's findings. Vandeplassche describes the cervix as open and freely secreting mucus in the typical case, but does not make it clear whether these are personal observations. There is thus a distinct gap in knowledge, resulting from other workers' inattention to the state of the cervix, especially with regard to the case in active œstrogen production. It would be consistent with the Hancock theory, if the free discharge of mucus in Garm's series were to prove most

characteristic of those of his cases with some retained cyclic tendency. In contrast, five authors, Koch and Berger, Garm, Vandeplassche, Laggi, and Roberts, describe clearly, as characteristic of nymphomania, the swollen vulva typical of normal œstrus. Vandeplassche also describes, in many undoubted *nymphomania* cases, which will " stand " as well as " jump," etc., an enlargement and swelling of the clitoris, as discussed above under *" adrenal virilism."*

The Blood Picture: In the realm of serology, Wayman and Asdell (1951) found that nymphomaniac cows had higher total serum protein concentration more consistently than controls, due to a rise in β and γ globulins only. This result seems to fit in with Szego and Roberts's report (1946) that two-thirds of the circulating œstrogen in the blood is " closely associated with the protein fraction." Presumably the increased globulins detected by Wayman and Asdell are required to carry the additional œstrogen burden.

General Physical Features and Behaviour: Bellowing, as a general feature, is noted by most of the clinical observers. Comment has been directed already to the frequent failure to particularise its *pitch,* and to distinguish this feature from its loudness, though it is described, sometimes rather loosely, as " bull-like," by Garm, by Sonnenbrodt and by Laggi (1955). Relaxation of the pelvic ligaments, resulting in the raising of the tailhead, is the most constant feature described by all the clinical observers quoted. Paredis and Vandeplassche (1953) recorded it in 94 per cent of cases. Garm, the most thorough investigator, confirmed this predominance in his material, and was able to correlate its degree, directly with the extent and duration of œstrous behaviour by the subject. His observed remission of relaxation in the terminal stages of disease has been mentioned, resulting from eventual atrophy of the œstrogenic ovary tissue, but Garm did encounter a number of cases showing no heat signs in which, nevertheless, the relaxation of the ligaments was quite marked. Roberts observed relaxation impartially both in nymphomaniac and anœstrous cystic cases.

A progressive unthriftiness is recorded by Garm, and by Sonnenbrodt and Ranninger who mention that it continues despite efforts to feed the subjects extra well. The latter authors also describe the progressive weakening of the (pelvic) bone structure, with ready tendency to fracture, as in the older literature. Curiously, this was conspicuously absent from Garm's material. The alteration in milk and meat properties has been discussed previously.

Behaviour is classified by Garm into the exhibition of continuous heat, regular heat, prolonged heat of reduced intensity, and absence of heat. It is stressed by this author, and implied by Vandeplassche, that the animals " stand " as well as " jump." The occurrence of heat at irregular intervals, often mentioned in the older literature, is described by Koch and Berger as characteristic of the early stages, but later it becomes continuous. Roberts described 70 per cent as nymphomaniac and the remaining 30 per cent as " anœstrous," and Berthelon makes the same sharp distinction. Romiti confirms Garm's observation that a proportion—though in his view a small one—does exhibit heat at regular intervals, but " usually heat is either irregular or absent." The behaviour as described by Sonnenbrodt is anomalous, presenting many bull-like features in the earlier

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continuous œstrus phase, which passes into one of anœstrus. Vandeplassche, too, decribes the development occasionally of aggressive tendencies, although the cows will "stand," have relaxed ligaments, and "slime" freely.

"Intermediacy": masculising effects alongside œstrogen production.

That such effects do occur, as distinct from those of true adrenal virilism, was recognised first by Vandeplassche (1951), and is abundantly confirmed by much of the other work, both later and earlier, from which indeed the existence of the phenomenon first became apparent to the present writer (independently of his own experimental observations). The clearest evidence of co-existence with œstrogen production is provided by the observations of Koch and Berger, and the American surgical experimenter Casady (1949), as well as Vandeplassche. Koch's detailed description of the cases he encountered enables the adrenal virilism cases to be differentiated clearly from those with free œstrogen production, in which milk yield temporarily rose on rupture of the thin-walled cysts, the vulva was swollen, and "chronically œstrous" behaviour was evident. Yet in these cases also, the masculising changes in the body contours were equally apparent, especially of the neck and haunch. In the photographs, this is most striking. Casady's descriptions of five cases studied, read like those of typical virilism, but urine androgen excretion was uniformly subnormal and directly comparable with Garm's results from typical nymphomaniacs. Vandeplassche considered that some 40 per cent of his nymphomaniacs, clearly distinguished from virilism cases, showed some masculinisation, of which the hypertrophy of the clitoris described above was perhaps the most striking, but which also included thickening of the neck and head and "masculine use of the horns." Paredis and Vandeplassche (1953) use the phrase "hyperœstrinæmia with masculinisation," a term at once accurate and expressive. Besides Sonnenbrodt's graphic description of bull-like behaviour in cows which become progressively thinner, as recorded by Garm under nymphomania, Laggi's definite observation of a lowered head-carriage, accompanied by allegedly bull-like bellows, relaxed ligaments, œdematous vulva, and thin-walled cysts responding well to LH therapy, may be referred to. Similarly, Bareggi records "the development of masculine body characteristics" in six heifers so responding after 20 to 30 vain services. This recalls Hancock's direct statement that he has cured cases of "*virilism*" by the same method. Finally, in connection with intermediacy, Garm's photograph of a true virilism case should be recalled. It shows the distinctly raised tailhead, the natural consequence of relaxed pelvic ligaments, which according to him is "the most constant and prominent sign of nymphomania," a perfectly correct conclusion. Garm's text contains no reference to the raised tailhead in virilism!

Besides Garm's finding of appreciable androgen excretion in normal control cows, Turner (1948) regularly recovered androgens as well as œstrogens in normal fæces, and Pigato and Guzzonato recorded them in milk (1955). Casady, whose results, on diseased cows only, paralleled Garm's, found in addition that unilateral adrenalectomy altered the excretion rate, while Gassner (1951)

followed up this hint and directly demonstrated the production of two or three separate androgens in the adrenal cortex of the normal cow. Turner suggested the joint production of the two antagonistic hormones might be some form of balancing mechanism. He mentioned that œstrogens affected the cortex, but it was Hancock (1949) who put forward the statement that follicular œstrogens promote cortical androgen secretion; thus further particularising the mode of operation of such a mechanism. Hancock made the point (see above) that the intervention of progesterone protected the cortex against continuous follicular œstrogen stimulation. Thus when, as in nymphomania, the proliferative phase in the ovary becomes chronic, it is easy to understand the cortical hypertrophy observed. It also becomes possible to interpret the luteinising effect of androgens, in the rat experimentally, and clinically in the cow affected with virilism, mentioned by Garm, as a protective reaction; in the case of virilism, to the excessive cortical androgen secretion. It is difficult to see where the two pathways diverge, following the initial excessive stimulation of the cortex by the follicular œstrogen, to produce respectively, typical nymphomania with reduced androgen secretion, and typical adrenal virilism. It is easy to appreciate that in the early stages there is frequently active production of follicular œstrogen, simultaneously with heightened androgen production by the stimulated cortex, thus accounting for the symptoms of "intermediacy" described in the preceding paragraph. It would be of interest in this connection to have a series of androgen estimations of urine, etc., from such intermediate cases as these, in which œstrogen production is clearly demonstrable. Vandeplassche has enunciated the alternative view that in intermediate cases the "testosterone" is secreted by the follicle, since Gaarenstroom (1946) claimed to have demonstrated the presence of this hormone in the normal ripening follicle. Some indirect support comes from Heard and his co-workers (1954), who suggested, because they found a pregnant mare could change injected testosterone quantitatively into urinary œstrogen, that this androgen was a physiological precursor of œstrogen, and so presumably was of follicular origin. It must not be forgotten that progesterone has been identified in the normal ripening follicle (see Hancock, 1949) and that progesterone and testosterone are chemically very similar. It is relevant also to recall that L. Berger (1945) pointed out that the androgens produced by the human adrenal in hypertrophy were chemically more like corticosterone than were other forms of androgen, and they were in this way distinctive. This hint of a possible chemical differentiation between the secretion sites of androgens does not appear to have been exploited any further.

Incidence of Disease by Breeds, Percentage Incidence, and Economic Importance

Garm declared the disease to be economically decidedly important, since "a considerable number of cows are slaughtered from this cause at the time of their best production." No clear figure on incidence, per cent of the cow population, was provided by him, but on the basis of 331 Red Swedish cases, and 102 in Friesians, he found in the former breed that cases most often develop in the second, and in the latter during the third lactation. The over-all incidence

means were respectively in the third and fourth lactations. Thus there is a more marked predisposition in the Red Swedish, though in both breeds the condition starts most commonly in the second to third month after calving, just when the milk yield approaches its peak. Eriksson (1948) found the disease to be quite common, allegedly economically important, in the Swedish Highland breed also, but also he gives no over-all percentage incidence.

Vandeplassche seemed to find no difficulty in locating numerous cases to study in Belgium, but he does not specify the breed or estimate the over-all percentage incidence. He agreed that the highest incidence was in the third to fourth lactation. Roberts (1955) is more informative, noticing a decided rise in the incidence, steadily over the 10 years to 1953. He found the disease to develop perhaps slightly earlier in the lactation than did Garm, quoting a period of 30 to 90 days after parturition, during which it was first manifest. The only hard figures that seem to be available on incidence are of limited application. One set refers to a particular Friesian herd in the United States (Casida and Chapman, 1949), in which over 10 years 7 per cent of the cows, 3.4 per cent of the heifers, exhibited cysts in any one year, and 19 per cent of cows developed them sooner or later. Two other sets of figures refer to abattoir surveys in Southern Germany in 1952. Gruber's material mostly comprised the German Red Spotted Mountain Breed; not fewer than 72 per cent of the cows and 28.6 per cent of the heifers had been discarded for failure to breed. The incidence of cystic disease was low, comprising only 5 per cent of the infertile cows and 16 per cent of the infertile heifers. Husbandry conditions were in this area, however, somewhat atypical, the great majority of the units consisting of fewer than five cows, while the owner had a full-time job elsewhere. Hoeckner by contrast found only 35 per cent of his 413 cows to have been discarded for infertility, of which a higher proportion, over 14 per cent, and thus about 5 per cent over-all, were cystic. This was slightly more than Gruber found. The breeds were not specified, nor the husbandry. In the main, cows which had completed only two to three lactations were involved, as compared with four to five for cattle discarded for other infertility reasons. Berthelon's French figures give a result on incidence quite at variance with all the foregoing, for he encountered only one case of the disease in the last 200 barren cattle he studied.

The Japanese Black breed provided most of the cases studied by Yamauchi and his associates (1954*c*), who found the incidence of cystic disease to be 9.7 per cent of all barreners. Sonnenbrodt's Austrian material was of the improved mid-European white breed. Bareggi (1953), Romiti, and Laggi have reported numerous cases of the disease from Italy, in breeds not always specified, while it certainly occurs in Hungary (Hirt and Szeky), Great Britain (Hancock, 1947), and Switzerland (Grandchamp, 1953, and Ruegg, 1949).

As will appear, ultimate prognosis seems worse in true adrenal virilism than in nymphomania. This possibility may justify an attempt to assess the proportionate incidence of virilism to the more common condition. Garm's figures are the most firmly based, fully worked out as they are with regard to all the organs concerned. They show 62 nymphomaniac and 14 adrenal virilism cases studied

in detail, including histology and clinical examination. He had some data about 433 other cases, about which forms were circulated to be completed by farmers and practising veterinary surgeons. This seems to have misled Vandeplassche, who reports Garm as having found 350 nymphomania cases along with his 14 of virilism. Apparently Vandeplassche missed the significance of the luteinisation of the cyst, rightly emphasised by Garm in the virilism cases. But the results of such an acute clinical observer as Vandeplassche must be accepted when he judges that virilism must be very rare in Belgium. He quotes the interesting experience of a practitioner who spayed 4,000 nymphomaniacs in a lifetime and found only 5 per cent quite unaffected by the operation. These were presumably the virilism cases with active adrenals. Unfortunately, Koch and Berger did not go beyond estimating their virilism cases as " a small proportion " of the whole. It may be justifiable to quote Bareggi's 20 Italian cows with small ovaries and 70 with large follicular cysts, all 90 of which responded to LH treatment, as representing respectively virilism and nymphomania cases. In this event the proportion is very similar to that which Garm found.

As luteal cysts appear to be genuinely characteristic of virilism, their proportions relative to the follicular type may not be irrelevant, in absence of further data specifically relating to virilism. Hoeckner found five cases of luteal cysts out of 20; Eriksson admitted to " a small proportion." Yamauchi and Inui had five cows which had either luteinised or thin-walled degenerate (non-secretory) cysts, to 19 nymphomaniac cows.

Except for Belgium, there is a remarkable general agreement (that is, from Scandinavia, Germany, Italy, Japan) that the proportion of luteal cyst or virilism cases to active nymphomaniacs is approximately 1 to 4.

Ætiology

As early as 1939, Eriksson had been able to prove, for the Swedish Highland breed, that a strong *tendency* to develop cystic ovarian disease was *inherited* from mother to daughter. Nine years later he published figures showing the daughter-dam relationships of 1,347 cystic daughters. Cystic dams produced 25.2 per cent cystic daughters, while normal dams produced only 12 per cent. Garm made similar, even more convincing, deductions on his Red Swedish and Friesian material, and concluded that the position in this respect was basically similar, for all three breeds, as maintained in Sweden. Vandeplassche was in accord with this general view, 9 of 45 cases he treated having affected dams, and contributed the observation, from the Belgian material, that 40 per cent of his cases that " recovered " on treatment, relapsed following the next calving, confirming the existence of an inherent tendency to the disease. Romiti noted that " several " of the 43 cases he studied in Italy belonged to one cow family. Gruber considered that the high incidence of the disease in his slaughter heifers, 16 per cent as compared with 5 per cent in cows, provided evidence that heredity was the most important ætiological aspect. Evidence of a different and more definite type was provided independently by Sonnenbrodt and Ranninger and by Koch and Berger. Each showed an undeniable inheritance of a well-marked syndrome, involving in the latter case both extremes of the disease, through a particular bull.

The circumstances strongly suggest that the gene appeared during the present century as a mutation. Evidence was clear that in Sonnenbrodt's "outbreak" the character was transmitted as a recessive and in Koch's as a partial dominant, and the breeds were respectively white mid-European and red-spotted German, so that the outbreaks were absolutely disconnected. (There is, however, every possibility of a connection between Gruber's material and that of Koch, as the same breed and locality are involved.) Circumstances in both breeds made the gene difficult to eradicate through selection. In the Koch and Berger A.I. undertaking, the affected animals responded so well at first to cheap treatment, rupture, and were such an improvement on non-affected sibs as dual-purpose cattle, that the farmers actively opposed any such attempt! Further work may reveal similar direct inheritance, in breeds and countries where only the less definite type of evidence, for a hereditary factor in causing the disease, has been recorded hitherto.

The case against the hereditary factor as a cause of cystic disease has been argued by Casida and Chapman, by Wille (1950) and by Fett (1953). Casida's very able work, in the single Friesian herd studied over 10 years, led to the conclusion that cystic tendencies were not directly heritable, but that long life-span was, and that a cow was the more likely to develop cystic disease in proportion to the length of time she had spent in the herd! Wille claimed that if the tendency to disease were heritable no dam of a subject would remain unaffected. He was much struck by the allegedly cystic condition in the ovaries of a series of 100 calves, 3 to 13 weeks old, and considered he could also recognise the characteristic changes in their skulls, necks, and facial expression. He accounted for the "disease" on the score of placental malnutrition during intra-uterine life. But Wille did not deny that a general poor breeding tendency could be inherited. Fett made a special study of inherited factors influencing infertility in dairy cattle and could find no evidence at all that cystic ovarian disease played any part, so far as the material that he was able to study was concerned.

There seems every reason to suppose from the evidence reviewed above, and indeed as Vandeplassche stated, that, endocrinologically speaking, the primary lesion takes place in the anterior pituitary gland, even though the scanty evidence we possess seems to show no abnormality here in terminal virilism cases. It is equally clear that the disturbance is in the rate and/or relative proportions secreted of LH and FSH, and Yamauchi illustrated in quite a striking manner that this proportion was 1 : 1 in controls and 1 : 3 in nymphomaniacs. It is unresolved whether an excess of FSH or a deficiency in LH is usually involved; though Paredis and Vandeplassche mentioned the latter, the increase in basophile type cells observed by Garm and by Yamauchi suggests a raised output of gonadotropic hormone and thus especially of FSH. The thin luteal linings of some cysts observed by Garm, and islets of luteal tissue in other cases, suggest that LH production may sometimes continue at about the normal rate, if the cases concerned exhibit evidence (through the urine excretion for example) that adrenal androgen production is below normal. The question is opened, whether any suggestion can be put forward with regard to the influence which precipitates abnormal development in the hypophysis.

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Effects of Environment: Nutrition: Samuels (1947) has produced some direct evidence, that the function of the anterior pituitary was affected readily by nutritional deficiency, and Hignett (1950) has, besides obtaining some indirect confirmation of this for the cow, linked it with seasonal fluctuations in, for example, the calcium and phosphate intake, dependent as he has shown, *inter alia,* on the rainfall and perhaps artificial manuring. Garm remarked about cystic disease that its incidence in Scandinavia varies from year to year, so that an environmental factor must be involved in addition to the hereditary one, which observation at once recalls those of Hignett. Grandchamp, too, associated the development of his nymphomaniac cases with " excessive " use of synthetic nitrates on the land, and Wille stated that unbalanced minerals and excess of protein were being fed to the dams during whose pregnancy he thought the disease developed. Roberts noted that a full half of his 352 cases developed from December to February—the very period when, according to Hignett (1953), reproductive efficiency is depressed by the exhaustion of vitamin D reserves accumulated during the previous summer. So it can be advanced with some confidence as a hypothesis that it is a failure of nutrition, possibly on the mineral/vitamin aspect, that precipitates the pathological change in the pituitary.

Milk yield: In view of the relatively constant composition of milk, and the wide natural variation in the diverse elements composing the various feeding stuffs, it is clear that a high-yielding cow will run a much greater risk than a poor yielder of exposure to inadequate nutrition. And it has in fact been found, in accordance with such a view, that cystic ovarian disease affects mainly the best yielders. This is additional evidence for the general nutritional hypothesis. How the disease strikes most often, just as the animal reaches the peak of its yield, has already been discussed. Vandeplassche noted the disease " did not occur in beef cattle," and was particularly a problem of the best yielders. Eriksson proved that the average yield of nymphomaniacs was notably higher than that of the corresponding normal cattle. Garm more significantly found that 45 per cent of his cases were the very highest yielders *on the basis of the individual herd averages,* and thus, by implication, throughout their lives. Only 7 per cent of the 433 cases he studied were poor yielders throughout their lives on such a basis. Casida and Chapman found that the incidence of the disease rose from 6.8 per cent to 10.6 per cent as the number of time cows were milked daily rose from two to four. This strongly suggested that the higher incidence affected the deeper milkers, and Danelius noted a much-above-average incidence in one large herd intensively managed for production.

Conclusions: It is undeniable that probably more of the highest yielders remain unaffected than develop cystic disease. It is the existence of a fair proportion of such cows, which " can stand the pace," that permits the continued pursuit of such intensive management policies as Danielius showed can result in a heavy crop of disease cases. Garm's differential observations, as between the Red Swedish and Friesian breeds, may provide the clue to some measure of explanation. The Red Swedish breed representatives developed the disease as a rule after two lactations, whereas the Friesians remained normal until after

three, suggesting greater resistance powers on the part of this breed. Now this result is not inconsistent with work by Lousse and Cordiez (1954) on feed conversion ability in the Fresian as compared with the Jersey breed. Their findings showed that the Friesians varied much less about a mean conversion-ability—" doing capacity "—than did the Jerseys. On the assumption that as many high yielders as poor ones have poor doing capacity, and that the Red Swedish, like the Jerseys, vary more about the mean than do the Friesians in this respect, the fact that not all high yielders develop the disease can be accounted for, as can the greater susceptibility of the Red Swedish, since it is the high yielders with *poor doing capacity* that are most liable to be inadequately fed, and so to develop hypophyseal pathology. Eriksson and Vandeplassche have both remarked that what seems to be inherited is a " weak endocrine constitution " a phrase coined by Lagerlof (1949, etc.). It is by no means impossible that such a " constitution " may be the result largely or entirely of " poor feed conversion ability," in which case the latter phrase could more accurately replace the former.

There is currently, especially in Great Britain and the United States, great emphasis placed on quick maturity and high yielding as qualities of dairy cattle —as the development of progeny testing, for instance, exemplifies. This is perhaps being done without much regard to " doing capacity " or longevity, so that, in the light of the natural history of cystic ovarian disease as now reviewed, a steep rise in the incidence of the disease can reasonably be expected. This has actually been observed by Roberts over the last 10 years in the N.E. United States. Probably the disease may prove to be more important economically than the incidence figures that are now available would indicate. There would appear to be a real need for more data on its relative importance, especially in this country and in breeds other than the Friesian, in which it may be relatively less important than in, for instance, the Jersey, which was found by Lousse and Cordiez to vary much from one cow to another in " doing capacity." It may be no coincidence that the evidence for inheritance of the disease was less strong in the Friesian material already studied. Possibly selective culling had in this herd eliminated the few " much-below-average doers."

Experimental Induction: The disease has been reproduced experimentally frequently either by œstrogen or by androgen administration. Laggi did so unintentionally in two cows to which he administered single normal clinical doses of stilbœstrol. These two did not respond to subsequent treatment. Hancock (1947) also records two cases similarly produced, but in one, and possibly both, treatment was effective. Wayman and Asdell produced a case deliberately by solid stilbœstrol implant. Cseh and Paal (1954) produced the disease in one of three cows given 100 mg. " Syntestrin." Yamauchi (1954*d*) succeeded in the case of three cows, again using stilbœstrol. One of the three proved decidedly more resistant to the drug than did the other two; she received 8 million i.u. in 20 injections over 50 days, and developed cysts 38 days after the last injection, recovering spontaneously 26 days later. This wide variation in sensitivity suggests that some of the subjects must have been, originally, much nearer the threshold of interference required to affect the pituitary than were others. This would

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presumably apply particularly to Laggi's and Hancock's cases, which received the stilbœstrol as treatment for some form of functional infertility already existing, which may be supposed to have been itself of nutritional origin and thus to have had a pituitary reaction. The direct "œstrogen shock" can undoubtedly damage the gland just as can imperfect nutrition, but in a thoroughly healthy subject, such as Yamauchi's third, which was apparently of a "strong endocrine constitution," this shock had to be very severe and even then did not have a lasting effect.

Therapeutics

The question of the effectiveness of treatment for cystic ovarian disease has been complicated by the fact that the incidence of endosalpingitis is very high in "barrener discard" cattle, and indeed generally in cattle with an infertility history. The present writer (Dawson, 1956) showed that it was present in 53 per cent of 200 "barrener discards" studied, so as to preclude all possibility of breeding on the affected side, and often occurring on both. Many investigators of the therapy of "nymphomania" have used "barrener discard" material. Casida, McShan and Meyer (1944) actually took some steps, and not without effect, separately to assess the effects of this treatment, in straightforward cases and those complicated by salpingitis, and Hancock (1947) was aware that this disorder affected the interpretation of his results; but Vandeplassche, Grandchamp, Laggi, Yamauchi, all report proportions of their treated cases, varying from 20 per cent to 50 per cent, in which a return to a normal ovarian cycle, without subsequent conception, was secured, without appreciating the probable reason for this disappointing result.

Treatment by Manual Rupture: This obvious and easy treatment, enucleation of the cysts by the hand per rectum, was being carried out certainly 80 years ago in Switzerland (Ruegg). Danelius (1944) obtained a measure of success by a single intervention, and Vandeplassche (1951) reported that about 40 per cent of all pregnancies secured by him, that is 18 per cent of animals treated, were thus brought about. Sonnenbrodt and Ranninger report a certain proportion of successes from rupture on one occasion only. But as 60 per cent of Vandeplassche's pregnancies, and many of Danelius's, followed one or more repetitions of the treatment, the suggestion presents itself that repetition is usually necessary; and only the repeated form of treatment by rupture is considered by Marshall and Hammond, Koch and Berger, and by Laggi. Marshall and Hammond (1937) recommended a routine return one week after the initial rupture to burst the follicle that was then usually present, whereupon a corpus luteum was formed, and a potentially fertile heat followed its waning. Laggi considered that as a rule treatment had to be repeated quite a number of times, requiring months of work on the same animal to be at all effective; and Latteur (1939) described rupture as merely a palliative. On the other hand, Laggi thought it a treatment still worth using in mild cases, Ruegg considered it highly effective, and in the outbreak of disease reported by Sonnenbrodt and Ranninger it was discovered to be so good a treatment that one practising veterinary surgeon ended by devoting

the whole of his time to its application! Koch and Berger secured pregnancy by this means in 19 of 27 cases, although there was a hopeless recurrence three years later in one of them. Danelius's over-all result gave a similar proportion, 67 per cent of pregnancies. Danelius matched this treatment against the use of hormones and considered it much superior, and that hormones were never worth using alone. Vandeplassche in 1951 took the same view. His material may well have included an unduly large proportion of salpingitis cases. Little is on record about the mechanism by which this treatment can be supposed to take effect. The superior efficiency of *repeated* treatment suggests, as one might expect, that the pituitary lesion resolves only slowly, on the removal of the excess œstrogen from the system. Presumably the prime cause of this lesion has been removed fortuitously in the meantime, as for instance by "curing malnutrition" through drying off the cow, and the dysfunction of the cells has since been maintained by the climate of œstrogen excess, just as in the experimentally-produced form of the disease. There is a distinct gap in knowledge about what takes place in the ovaries during the few days following rupture. After a week, Vandeplassche found most often new cysts, sometimes a quite normal follicle, sometimes a luteal body.

Hormonal Therapy: Latteur in 1939 used undifferentiated anterior pituitary extracts, as did Casida, McShan and Meyer (1944), in a dose equivalent to one gramme of sheep pituitary. Roberts, too, made some use of this preparation, and he also used pregnant mare serum, as did Moore (1946), in a dose of 1,000 i.u. Grandchamp used progesterone, 225 to 300 mg., and Runge (1942) tried bull testis filtrate, presumably testosterone, on a few cases. The majority have, however, used differentiated extracts, with some concentration of LH, usually from human pregnancy urine, although only Romiti, Yamauchi, and Roberts emphasise the source. Danelius used a standard dose of 600 i.u., although this was sometimes repeated to give a total of 1,200 to one animal. Hancock (1947) used 800 to 3,200 i.u. and Bareggi (1953) 1,000 to 1,500 i.u., which he sometimes had to repeat after 15 days. Paredis and Vandeplassche used 250 to 1,000 i.u., while Romiti and Laggi both write that dosages of 10,000 i.u. were employed, Laggi grading up to this by quarter and half doses. Possibly Romiti and Laggi refer to a unit ten times smaller than the others. Yamauchi used 10,000 "international mouse units," possibly the same measure of dosage as these two Italians administered. The intravenous route has been used in most cases, following the lead of Casida, who emphasised its importance, but Danelius and Grandchamp used the intramuscular route, as did Romiti, and Laggi for the larger doses. Roberts gave p.m.s. subcutaneously, while Runge, and Paredis and Vandeplassche, injected direct into the cystic follicle.

As regards results, Latteur claimed "very satisfactory ones"; Casida, *et al.*, obtained 35 pregnancies from 53 cows served (excluding his "salpingitis" group); Paredis and Vandeplassche 36 out of 59 services. Moore claimed 66 per cent conceived of those treated, while Roberts obtained a similar figure with the same drug, p.m.s., but 80 per cent both with sheep pituitary and LH (PU). Grandchamp had four conceptions, and three others that improved, of 11 cases.

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Laggi obtained 50 per cent pregnancies on 18 cases, with a further proportion (possibly salpingitis) in which a normal cycle was restored, and a "butcher's cure" was achieved, restoring to normal the value of the carcase. Bareggi claimed 85 per cent pregnancies on 70 cows with large cysts, using up to 3,000 i.u. Hancock restored a normal cycle in 11 to 12 cases and obtained seven conceptions in nine services. Seven out of nine of Yamauchi's cows served, conceived. As far as the evidence goes, it would appear that sheep pituitary is as good a source of the curative principle as is LH (PU), and that intrafollicular injection is no more effective than intravenous. There is a hint, from Danelius's poor results with a low dose intramuscularly, that Casida's insistence on the intravenous route has justified itself, though Laggi had reasonable results intramuscularly. Although occasionally 500 i.u. has proved effective, a strong case may be made out that 1,000 i.u. is the smallest dose that is worth using. As might be expected, pregnant mare serum, which is a better source of FSH than of LH, proved less successful than the other hormone preparations, though the rather unnecessary precaution of subcutaneous administration may have handicapped its effect. No undeniable improvement in general results, such as might have been ascribed to the use of purer and better-standardised hormone preparations, has been apparent over the years; though it is true that Hancock (1948) reported a fairly high incidence of multiple ovulation following the use of LH, whereas Paredis and Vandeplassche (1953) found this risk to be a slight one. Yamauchi (1955) followed carefully the changes in the cysts following LH administration. Roughly one-third ruptured and luteinised, one-third luteinised without rupture, and one-third remained unaffected. The effect of treatment on a cyst appeared to depend on the survival of the theca interna, partially present as it was in the middle group, and totally degenerate in the unaffected cysts. In the next two to five days urinary œstrogen fell rapidly and the ambitious claim is made that "pregnandiol excretion in the urine rose to normal levels." The pituitaries of cured cows were analysed and found normal, but it is not made clear how soon after treatment these cows were slaughtered.

A theoretical basis for the effectiveness of progesterone therapy, as observed by Grandchamp, might be found partly in the protective effect it has been seen to have on the adrenal cortex, especially if "intermediacy" cases were involved, and conceivably, too, in some neutralisation of the effect of œstrogen on the pituitary. The moderate, but perhaps still surprising, therapeutic effect of pregnant mare serum must be ascribed to its limited LH content. Presumably the ovaries have been already so over-stimulated by endogenous FSH that by the time of treatment they are no longer able to be influenced by the greater content of this hormone in the drug.

Combined Rupture and Hormonal Therapy. There appears to be remarkably little evidence about the effectiveness of hormonal treatment in cases where rupture has failed; though Latteur wrote enthusiastically about this aspect, and Romiti claimed good results without giving exact particulars, all that can be said is that the field is a promising one for further exploration. Romiti's main

trial was of hormone therapy combined with rupture, and he claimed cure or amelioration in all cases, though without stating the proportion of pregnancies. Laggi deliberately tested the effect of hormones alone, against that of hormones accompanied by rupture, and concluded on 35 animals that most if not all the good results observed were due to the use of the hormone. Roberts, too, came to the same conclusion after studying a greater number of animals. By contrast Danelius tested rupture treatment alone, against rupture accompanied by hormones, and came to the conclusion that the hormones were useless, except possibly as ancillary to rupture in the odd case. 67 per cent of both groups became pregnant. But Danelius was using rather a low dose of hormone by the intramuscular route, which is probably less effective.

The slight and vague nature of the evidence about the good effect of hormones when rupture has failed has been noted, but such evidence cannot altogether be disregarded. Evidence is strong that both rupture alone, and hormone alone, can be effective treatments; equally strong, perhaps, that simultaneous rupture does not assist hormone therapy, but less convincing that rupture alone may not be less effective than when supplemented by hormone. The conclusion is, then, drawn that rupture, repeated at least once, should first be tried, at the same time correcting the malnutrition that is apt to be present. Should this fail, intravenous LH may be administered, in not less than 1,000 i.u. doses, and should this again fail, rupture together with lutormone may be tried, or progesterone alone or in combination.

Control of Treatment, and Prognosis. No mention has been found in the literature of any attempt to study the effectiveness of treatment by leaving untreated controls, except of the experimentally produced disease. The difficulties attending this step in a field experiment must be admitted, but they have been in the past much exaggerated, and have been twice overcome by the present writer (Dawson, 1951, 1954) among other workers. In the meantime, inference must be used to arrive at some estimate of prognosis, both without and in the presence of treatment. It appears that about 10 per cent of barrener discards have advanced cystic disease, and this probably means that one in four is so affected, if the cases barren from endometritis and salpingitis be ignored. Cystic disease thus has a strong tendency to progress into the hopeless stage. At the same time many cases have been observed to recover "spontaneously" probably because an unwitting change in the feeding stuffs, or in the season, has removed the precipitant nutritional cause before the pituitary reaction induced had passed the point of no return. Such observations are not thought worth publishing, unlike the results of treatment; generally good as these are seen to be, the possibility of selection of the best treatment risks cannot be ruled out in considering reported results. At present the prognosis can only be said to be variable, and largely dependent on the pedigree of the affected animal, its age, and its management for milk production: it is probably better when the case is treated, than when it is left to itself. Casida's cured cases had persisted two months at least before treatment, five of Bareggi's had been served 20 to 30 times, Yamauchi cured a case of eight months' standing, Paredis and Vande-

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plassche cured many of three months and several of six months, as did Romiti also. The Belgian workers, as also Sonnenbrodt and Grandchamp, did not shrink from publishing the obvious conclusion, that prognosis was better in cases treated early. Koch and Berger noticed that prognosis was poorer in their virilism cases, of which only one of nine bred again, and confirmation comes from Northamptonshire, Tutton (1955) having in the course of practice observed this distinction.

Summary

Most of the work has been done on the continent of Europe, with a notable contribution from Japan. There has been less interest in the United States and more especially in Great Britain. General agreement exists that two forms of the disease occur, adrenal virilism and the commoner "hyperœstrinæmia." The respective changes in the adrenal, anterior pituitary, ovary, excretory function, remainder of genital tract, blood plasma, external body conformation and behaviour are reviewed. Convergent independent testimony tends to establish that in the œstrogenic condition, nymphomania *sensu stricto,* there is change in the anterior pituitary basophil cells with some increase in their proportion. Stress is laid on the evidence that follicular cysts pass through a stage of active œstrogen secretion in which the theca interna and granulosa are hypertrophied; following this, secretion ceases and these layers degenerate. Nevertheless there is agreement that in a proportion of cases the condition of genuine hyperœstrinæmia can co-exist with a persistent ovarian cycle. It is shown that the bacteriological and histopathological aspects of the uterine pathology have largely been neglected and that the only study that has been carried out on these with any thoroughness gave atypical results; the condition of the cervix, too, is found to be a significant detail, the study of which has been markedly neglected.

Attention is drawn to the work of Vandeplassche (1951) who first pointed out that, quite apart from true virilism cases which, it seems, are outnumbered four to one by the others, a proportion of nymphomaniacs show a degree of "intermediacy" with some masculising changes. A considerable body of supporting evidence is adduced from other clinical reports to confirm this circumstance and the physiological background is considered in relation to these, affording some information on the inter-relationships of the different forms of disease, though androgen excretion does not yet seem to have been determined in cases showing intermediacy. Evidence on the highly significant question of over-all percentage incidence and economic importance is shown to be far too scanty; 5 to 10 per cent of barrener discard cattle are so affected, according to the available evidence, and there is agreement that usually the disease strikes early in the second or third lactation, and causes important economic loss. There is a strong body of evidence that the factor of heredity is important in the ætiology of the disease, which has twice been directly transmitted by individual bulls apparently as the result of a mutation. The interplay of this factor with that of environment is reviewed, and the significance is proved of high yielding ability taking effect through inadequate nutrition.

In the field of therapeutics, evidence is brought forward that manual rupture, and LH administration, 1,000 i.u. intravenously, can both be effective forms of treatment. Insufficient evidence is available on the effectiveness of hormone treatment when rupture has failed. It is possible that simultaneous use of hormone may improve the result from rupture therapy. No attempt has ever been made to leave a proportion of untreated controls; and there is no information on the ovarian changes during the first five days following rupture. A number of cases recover when disease has existed over six months.

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XUM

PLATE I

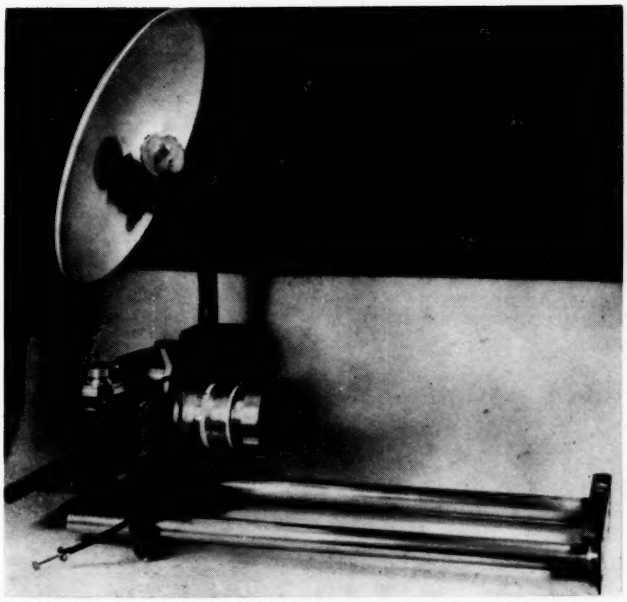

Fig. 1
The close-shot camera mounting ready for use.

Fig. 2
Using the apparatus to photograph a skin lesion.

(*Article by Lewis, page* 133)

PLATE II

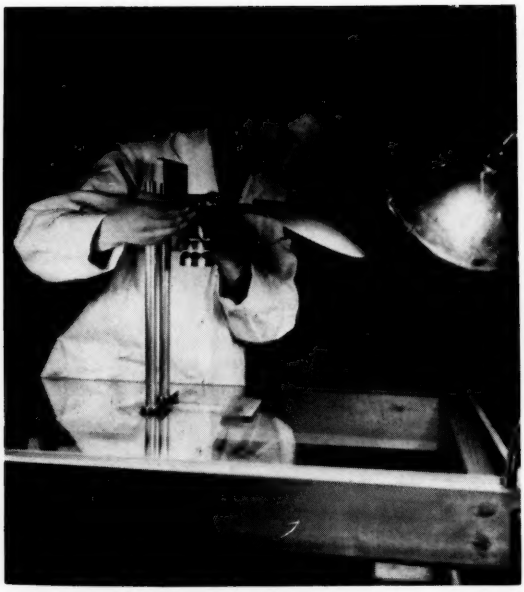

Fig. 3

Using the apparatus to photograph a specimen or document.

(*Article by Lewis, page* 133)

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A FIXED-FOCUS, CLOSE-SHOT CAMERA MOUNTING FOR VETERINARY CLINICAL PHOTOGRAPHY

By E. F. LEWIS, M.R.C.V.S.
Royal Veterinary College, Streatley

In almost every field of endeavour, the practice of some branch of photography has become necessary. The biological sciences are served well by a process able to record events which may be rare or fleeting in nature. The camera is a useful aid in teaching, research, and for reference requirements. It is relatively easy to depict static objects, but when one attempts to photograph a living animal or part thereof the task is not a simple one.

The greatest difficulty encountered in photographing any part of a fully-conscious animal is the maintenance of position once the working distance has been decided and the lens focused. The quietest animal may move away from or towards the camera as a natural reaction to restraint or at the sight of something which is novel or strange. The apprehension of hurt is liable to be an important factor. For this reason it has been found necessary to devise an apparatus to keep the camera at a constant distance and release the operator from long sessions of patient manœuvring between wasted efforts.

The simplest device consists of a measured piece of wood which is attached to the camera bosshead and extends forwards parallel to and below the axis of the lens. With the appropriate shutter and lens settings, the apparatus can be held in position with the end of the piece of wood pressed lightly against the animal just below the area being photographed. A single-lens reflex viewfinder enables the operator to obtain a correct view, and the picture can be taken successfully by keeping steady pressure against the animal, even when the latter moves. The main disadvantage of such a simple device lies in the lack of flexibility with regard to both size of picture and depth of focus. This difficulty was not overcome until a modified form of the apparatus described by Gibson (1954) for use in the human subject was devised. Gibson's apparatus has little greater flexibility than the simple device described above, but the modifications incorporated in the equipment provide for better adjustment.

The camera is mounted on a platform to which a flashlight apparatus is secured. The pressure plate is carried at the end of two rails which pass through

collars fixed to the front surface of the camera mounting. The distance is adjusted by focusing the camera on a page of print, and the camera rails can be locked in position by turning screws in the collars. The dimensions of the apparatus will depend on the focal length of the lens and the type of camera used, and can be decided by measuring the area covered at a given working distance. The pressure plate should lie about ½ to 1 inch below the field. The distance of this plate from the centre of the field will be known, and provided this is always maintained and the camera mounting kept at right-angles to the subject, the photograph can be taken easily and accurately.

With the short working distance which will be found to be needed, the smallest flash-bulbs provide adequate illumination when the lens is stopped well down. This provides considerable depth of focus even when comparatively long extension tubes are used. In the apparatus described, a Contax 35 millimetre camera with an f.2 lens has been used. The focal length is 5 cm., and for close shots a 1 cm. extension tube is fitted. The area of the field is approximately 6 inches by 5 inches. The pressure plate is fixed at 3½ inches from the central axis of the lens. As the shutter is synchronised accurately only at slow speeds, a setting of 1/20 second has been employed, and, with Kodachrome Type "A" film, apertures of f.16 to f.22, depending on the brightness of the subject, have given correctly exposed transparencies when Philips PF1, Class M bulbs were used. The flash reflector is directed towards the centre of the field. An electronic flash apparatus has not been used, but it would be a very useful modification, particularly if a lens-encircling tube is fitted.

The use of extension tubes precludes rapid change of working distance. This is a disadvantage in clinical photography as an average full clinical record should include close, medium and long shots of lesions and subject. This can be overcome by the use of supplementary lenses instead of extension tubes, the rapid exchange of these lenses being facilitated by "slip-on" mounts. At greater distances, higher-powered lamps and larger lens-aperture settings will be needed.

Further modifications may be devised to increase the efficiency of the apparatus. A black-and-white scale strip could be mounted on the pressure plate so that it could be included in the bottom of the photograph when close shots are made. This would, however, need to be detached when long shots are taken. It could, for convenience, be mounted on a hinged flap and folded out of view when not required. A second flash device could be fitted on the opposite side of the camera from the first if greater or more even illumination was required. With the apparatus described accurate pictures can be made without viewing the field through the camera view-finder.

Equipment of the type described can be manufactured in any small workshop. It is a most useful aid to a veterinary clinical photographer. Once the apparatus is fixed at the appropriate settings the equipment can be used by a person who has only an elementary knowledge of photographic processes.

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REVIEWS

FIRST AID FOR PETS, by Leon F. Whitney, D.V.M. London: Faber & Faber. 12s. 6d. net.

FIRST-AID books and instruction fall between two stools. They may accentuate fear so that every simple accident or ailment becomes a major occasion and the physician or surgeon is called from his bed at all hours, or they may do the opposite and give a layman the idea that he is competent to deal with any emergency. For the patient or victim the latter is the gravest fault for the professional man's services may not be sought until all hope that he might be able to do some good has gone. Leon Whitney's book steers a middle course and any intelligent layman who reads it should know what he can and cannot do. The author makes it quite clear when professional assistance must be sought.

There are chapters on restraint and the handling of accidental injuries, minor surgical procedures, first-aid in sickness and in poisoning. Some of his illustrations refer specifically to America; for instance, it is not likely that an "English" first-aider would be required to extract porcupine quills from the nose of a dog or have to deal with a dog which has been sprayed by a skunk. There is a useful chapter on parasitic control and no doubt any owner conversant with this part of the book would carry out the instructions of a veterinary surgeon with intelligent interest. Chapter 13, "The Last Aid," is well worth reading. The last two chapters are devoted to birds and fish and they contain items of information which may be useful to practitioners who are consulted only occasionally on the diseases, etc., of these patients. A glossary of common medical terms and an index which makes reference easy complete the book.

The book should serve a useful purpose in educating laymen in first-aid matters. It may also be of value to junior veterinary students who, because they have entered a veterinary college, are supposed by their neighbours and friends to be in possession of a profound knowledge of veterinary practice and its emergencies. A quick glance at the index may enable them to preserve their reputation.

CONTROL OF JOHNE'S DISEASE IN CATTLE, SHEEP AND GOATS. 1956. Published by European Productivity Agency of O.E.E.C. Paris. Pp. 202. Figures and tables. Price 2s.

In February and March, 1955, about 35 experts on Johne's disease, from ten O.E.E.C. member countries, and a representative from F.A.O., met at the Central Veterinary Laboratory, Weybridge, to discuss the control of Johne's disease in cattle, sheep and goats. The present publication includes papers presented by guest speakers as well as a basic report prepared by the Central Veterinary Laboratory, Weybridge.

The Chief Veterinary Officer of the Ministry of Agriculture, Fisheries and Food, J. N. Ritchie, gave an interesting address in which he explained how Great Britain was served by her veterinary surgeons; he paid special attention to the organisation of the official veterinary services and their duties and facilities for research. The animal health situation in Great Britain received some attention,

and so the foundation was laid for introducing the difficulties of controlling Johne's disease. It is, as he pointed out, " a disease so insidious that but a proportion of infected animals develop clinical symptoms, fatal once scouring has become apparent, so wasting that salvage of the carcase is valueless."

The basic report, prepared by the Central Veterinary Laboratory, contains a useful account of Johne's disease in cattle, sheep and goats; it was emphasised that, in cattle, susceptibility to infection is greatest in the calf and the incubation period is long and is seldom less than two years. A large number of sub-clinical infections exist, and these animals may be dangerous to young stock; the longevity of *M. johnei,* which may live for nine to twelve months in dung, soil and pond water, complicates control measures. There is no diagnostic test which has met with universal approval. Complement fixation tests can be used only in tuberculosis-free herds because of cross reactions. Prophylactic vaccination is used extensively in France, and promising results have been obtained there and in England; no method of treatment is even moderately effective. Although no specific nutritional factor is recognised as of prime importance, it is considered that nutritional influences may decide whether an infected animal becomes a clinical case.

The disease in sheep is complicated by the possible plurality of types of Johne's bacilli involved and the variety of lesions which may be found; vaccination may be an effective method of control. The goat may be infected naturally and experimentally and the natural disease may be of greater economic importance than is generally appreciated.

The discussions were preceded by papers dealing with the bacteriology, pathology and transmission of the disease in cattle, its epidemiology and methods of diagnosis, and its control. It is possible that a bacteræmia may occur in the natural disease and, if so, then this would account in some measure for the occasional case of congenital infection and for the rare presence of the bacteria in udder tissue. It is noted, by transmission experiments and by observations of natural cases, that susceptibility is greatest in the young calf and that a latent infection or a clinical case may develop. The spread of infection is largely through the medium of water, food, straw or milk contaminated with infected fæces. Clinical signs may appear in latently infected animals under the influence of gestation, parturition, the nature of the soil or some nutritional deficiency. A study of the epidemiology of the disease is an aid to diagnosis; in tuberculous herds the value of allergic and serological tests is limited, but they have an enhanced value in herds free from tuberculosis. Microscopic examination of fæces is a simple test, but repeated examinations are necessary as negative results cannot be accepted as such.

It was emphasised that every effort should be taken to prevent the introduction of infection by imported stock. It is a difficult disease to control, and in those countries where infection exists, attempts should be made to establish herds free from disease or, alternatively, recourse should be made to vaccination. Clinical cases should be isolated or slaughtered when consideration is given to individual infected herds, and calves should be moved from infected environ-

ments; the complement fixation test may be used as an accessory means of diagnosis.

Two papers were presented on Johne's disease in sheep, and it was suggested that further observations as to its presence should be made by abattoir examination. All three varieties of Johne's bacillus, which may be found in sheep, are infective for cattle, and precautions should be taken to avoid cross infection. Vaccination is advocated as a method of control, especially as its effect on the tuberculin test is of no practical importance in sheep.

The preface to this report includes a hope that " this publication will provide a valuable source of reference to member countries and make also a useful contribution towards increasing productivity in this sector of European agriculture." This is not a vain hope; the publication provides one of the best accounts of the control of Johne's disease in existence.

PRACTICAL SHEPHERDING, by H. G. Clark. London: Farmer & Stockbreeder Publications Ltd. Price 7s. 6d.

A SMALL book which will fit conveniently into a jacket pocket, yet containing a wealth of useful information. It is written in the simple and lucid style that one expects from a man who is a master of his job. It will be appreciated by an experienced shepherd and understood readily by a novice.

It guides one through all the facets of sheep management from the foundation of a flock to marketing. In recent years the craft of the shepherd has been in a decline and there is a dearth of the type of man whose knowledge was founded on traditional custom and his own experience. Much of this knowledge was passed on by word of mouth, and this little book will do much to fill the void.

It should be very useful to veterinary students when they are pursuing their studies in animal husbandry.

THE AFRICAN VETERINARY HANDBOOK, by P. Z. MacKenzie and R. M. Simpson. Sir Isaac Pitman & Sons Ltd. 18s. net.

THIS book is intended for the instruction and guidance of African stock owners, etc., who live in remote areas where skilled professional aid is not always available. There is much also in the text which can be of great value to a veterinary surgeon, especially to one who may be new to Africa and is not familiar with the special diseases of that continent.

An introduction which is remarkable for brevity and clarity deals on broad lines with the signs of disease, the causes, immunity, treatment and prevention.

The first eight parts or chapters of the book are designated according to the animals affected, i.e., Diseases of Cattle, Horses, Camels, Poultry, etc., and under these headings the various diseases to which the animals are subject are set forth in alphabetical order. This makes reference easy. The salient features of each disease, i.e., recognition, cause, treatment, etc., are discussed. Part IX deals succinctly with Parasites and the troubles they provoke, both internal and external. Part X is a farrago and deals with a variety of topics ranging from artificial insemination and bloat to saddle sores and tumours.

Part XI is devoted to simple first-aid measures and a list is given of the instruments, dressings and drugs which should be included in the first-aid chest.

A glossary and the index complete the book. The glossary should be most useful to the amateur veterinary surgeon.

This is a very useful book. It must be of great practical value to those it is intended to serve. A remarkable wealth of information has been compressed into its 281 rather small pages, and the authors should be congratulated for their brevity and clarity. Most modern authors lack these valuable attributes.

FIRST HUNDRED YEARS,
Pfizer Ltd.

It is just over one hundred years since Dr. Thomas Addison published his monograph on "The Constitutional and Local Effects of Diseases of the Suprarenal Capsules."

Addison's observations form one of the foundation-stones on which the science of endocrinology has been built. Addison dealt with the signs and symptoms of certain harmful effects which may follow an upset of the functions of the adrenal glands due to abnormality or disease. He, in his day, could only surmise that this structure which had no duct must give rise to or elaborate a substance or substances which was probably distributed by the vascular system of distant parts of the body. We know now that there are a number of other structures in the body which work their will in a similar manner and collectively constitute the endocrine system and the products of their activity have been called hormones. We know that these secretions have a profound influence in the normal body on growth metabolism and reproduction. Many hormones have been isolated and their chemical composition disclosed. In certain cases chemists have been able to synthetise them and the products of the laboratory can be used to promote action similar to those initiated by the natural product. The endocrine system has come to be known as the chemical regulator of the metabolism of the body. The endocrine glands work together and in harmony and any diversion from this linked system, even in only one of the structures, may evoke aberrations in the functions of the others with repercussions in distant parts of the body. By controlled experiment and also by the older system of trial and error we know that hormones can have a stimulating and beneficial action, when used with discretion, in the treatment of disease processes in parts which were not suspected as being under their particular influence. One of the best illustrations of this is the value of adrenal hormone treatment in certain lesions of the eye.

In recent years the adrenal hormones have been the subject of much investigation and as a result a therapeutic field, which is expanding constantly,

has been opened up. In common language the corticosteroids are front page therapeutic news and by making this booklet available to medical men and veterinary surgeons, Messrs. Pfizer have done a great service to both professions.

Endocrinology, and especially the chemistry of hormones, can be a most complicated science and to understand much of the work that has been published requires a profound knowledge of biochemistry. The ordinary professional man, long past the classroom, is at some disadvantage and we are sure that he will welcome and appreciate this book which, in simple and interesting language, traces the history of the adrenal hormones and gives the indications for their use. For those whose knowledge of endocrinology allows of a comprehension of the finer details of the biochemistry of the corticosteroids, the bibliography at the end of each section will be of great value.

CORRESPONDENCE

To the Editor,

SIR,

I have read with interest the article in your November, 1956, issue entitled "An Indigenous British Horse"—particularly as I am familiar with the Exmoors as well as practically all other British ponies. While in no way detracting from the Exmoor, various authorities are of the opinion that the Shetland pony is about the only indigenous breed in Britain.

Brian Vessey-Fitzgerald in "The Book of the Horse" states that the Shetland pony "was in the islands at least as early as the sixth century A.D. and in all probability very much earlier," and that "The Shetland pony stands apart from all others as an original prehistoric type." It would, therefore, be interesting to have an exhaustive study similar to that conducted on the Exmoors carried out on the Shetland pony.

The condemnation of the Tarpan (Equus prjwalsky) as mongrel appears rather sweeping. In Carl Hagenbeck's "Beasts and Men" (1909) these horses were said to be found in numbers in their wild state in the neighbourhood of Kobdo, Mongolia, a town situated under the northern slopes of the Altai Mountains and the terminus of the great caravan route from Pekin.

Hagenbeck further reproduced a photograph of a pair of wild horses and states that 28 arrived safely at Hamburg from Kobdo, Mongolia. The photograph bears no resemblance to "the degenerate horse of Asia" (Fig. 2) but rather resembles Fig. 3—"one of the typical wild horses."

Yours faithfully,

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J. M. FLETCHER, M.R.C.V.S.,
Assistant Director
(Veterinary).

NEWS

Alteration to Pack

BURROUGHS WELLCOME & Co. announce that "Wellcome" brand Leptospira Icterohamemorrhagiæ Vaccine is now issued solely in containers of 3 c.c. This pack contains sufficient vaccine for the recommended immunising course for a dog or fox.

No Increase in Price

ALTHOUGH faced with heavy all-round increases in manufacturing costs and in fuel and freight charges, as are other companies, Deosan Ltd. state that in the national interest and in support of their loyal customers, it will be their policy to hold their prices at their present level for as long as possible and they will make no changes unless forced to do so.

New Title

MESSRS. ALLEN & HANBURYS LTD. wish to announce that Allen & Hanburys' Canine Distemper Vaccine, Egg-Adapted (Living) is now being issued under the title "Kavol."

NOTICES

Appointment

IT is announced that Mr. A. N. McNamara, B.Sc., F.P.S., F.R.I.C., a director of Willows Francis Ltd., has assumed the additional responsibility of over-all supervision of Technical Research and Development Sections of Willows Francis Ltd., and their associated concern, Pharmaceutical Manufacturing Co.

An interesting visit

A PARTY of fifteen students and one lecturer from the Students' Union Society, Royal Veterinary College, paid an afternoon visit to Glaxo Laboratories Ltd., Greenford, on Monday, February 11. A talk and demonstration was staged for them by the company's Veterinary Research Unit and covered aspects of tissue culture, veterinary bacteriology and also methods of antibiotic assay. The demonstration was followed by a tour of the factory premises. The visitors also saw an example of documentary film-making—the Glaxo film "Defence Against Poliomyelitis" which describes the manufacture and testing of the company's anti-poliomyelitis vaccine.